Neuroimaging of cerebral small vessel disease

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Abstract

Lacunar stroke accounts for one quarter of all ischaemic stroke and in the long term carries a greater risk of death and disability than was previously realised. Much of our current knowledge originated from neuropathological studies in the 1950s and 1960s. In the last thirty years, brain computed tomography (CT) and magnetic resonance imaging (MRI) have revolutionised our understanding of lacunar stroke and associated features of cerebral small vessel disease (SVD), namely white matter lesions (WML), enlarged perivascular spaces (EPVS) and brain microbleeds (BMB).

The purpose of the projects which led to the writing of this thesis was to improve understanding of imaging characteristics of cerebral SVD. We aimed to assess (i) clinical and imaging features which might explain misclassification of lacunar infarcts as cortical infarcts and vice versa, (ii) the proportion of symptomatic lacunar infarcts progressing to lacunar cavities and associations of cavitation, (iii) completeness of reporting of lacunar lesions in the lacunar stroke literature, (iv) definitions and detection of lacunar lesions amongst SVD researchers, (v) the relationship between WML and carotid stenosis, (vi) clinical and imaging associations of EPVS and, (vii) observer variability in the assessment of EPVS and BMB, in order to develop visual rating scales.

Section one describes neuroimaging of lacunar stroke. To investigate features which might explain clinical stroke subtype misclassification ('clinical-imaging dissociation'), I used data from a stroke study. The main factor associated with clinical-imaging dissociation was diabetes, and in patients with acute lacunar infarction, proximity of the lacunar infarct to the cortex, age, diabetes and left

hemisphere location. To investigate the proportion of symptomatic lacunar infarcts progressing to cavities, I used data from two stroke studies. A fifth of patients with acute lacunar ischaemic stroke showed definite cavitation on follow-up imaging at a median of 227 days; cavitation was associated with increasing time to follow-up. To assess completeness of reporting of lacunar lesions in the lacunar stroke literature, I reviewed 50 articles from three journals with a stroke focus. There was marked variation in terminology and descriptions of imaging definitions of lacunar lesions. To assess lacunar lesion definitions and detection amongst SVD researchers, I used an online survey consisting of case-based and non-case-based questions. There was marked variation in definitions and descriptions. Cavitated lesions were detected with the highest degree of confidence.

Section two describes neuroimaging of associated features of cerebral SVD. Using data from two stroke studies, I examined the relationship between WML and ipsilateral carotid artery stenosis. There was no association between carotid stenosis and WML. I tested the association of EPVS with WML and lacunar stroke subtype using data from a stroke study. Total EPVS were associated with age and deep WML; basal ganglia (BG) EPVS were associated with age, centrum semiovale (CS) EPVS, cerebral atrophy and lacunar stroke subtype. Quantification of observer variability in EPVS rating was assessed on 60 MRI scans selected from a stroke study and an ageing cohort. Intrarater agreement was good and interrater agreement was moderate. Main reasons for interrater disagreement included the visualisation of very small EPVS and the presence of concomitant WML and lacunar lesions. Observer variability in BMB rating was quantified using MRI scans from a stroke study. Interrater agreement was moderate but improved following modification of the

pilot rating scale (BOMBS; Brain Observer MicroBleed Scale), which had its main effect by differentiating ‘certain’ BMB from ‘uncertain’ BMB and BMB ‘mimics’.

In conclusion, neuroimaging, particularly MRI, is a valuable tool for the investigation of lacunar stroke and associated features of cerebral SVD. With recent technological advances in both CT and MRI, neuroimaging will remain central to future SVD studies, hopefully leading to a much improved understanding of this important disease.

Declaration

I confirm I composed this thesis and that it is my own original work. I have not submitted any part of this thesis for any other degree or professional qualification.

Gillian Margaret Potter

5th March 2011

Publications and awards relating to the work of this thesis

Awards

1. Potter GM, Doubal FN, Jackson CA, Chappell FM, Sudlow CLM, Dennis MS, Wardlaw JM. Long-term appearance of lacunar infarction on imaging: what proportion become CSF-containing cavities. Winner of poster prize, British Society of Neuroradiologists Annual Meeting 2008.

2. Cordonnier C, Potter GM, Doubal F, Jackson CA, Keir S, Sudlow CLM, Wardlaw JM and Al-Shahi Salman R. Improving interrater agreement about brain microbleeds: development of the Brain Observer MicroBleed Scale (BOMBS). Distinction awarded for poster, European Stroke Conference 2007.

Papers in peer-reviewed journals

1. Potter GM, Roman G. Cerebral small-vessel disease: What lies beyond the early years? *Neurology* 2011;76:684-685.

2. Potter GM, Marlborough FJ, Wardlaw JM. Wide variation in definition, detection and description of lacunar lesions on imaging. *Stroke* 2011;42:359-366.

3. Potter GM, Doubal FN, Jackson CA, Chappell FM, Sudlow CLM, Dennis MS, Wardlaw JM. Long-term appearance of lacunar infarction on imaging: what proportion become CSF-containing cavities? *Stroke* 2010;41:267-272.

4. Potter GM, Doubal FN, Jackson CA, Sudlow CLM, Dennis MS, Wardlaw JM. Associations of clinical stroke misclassification ('clinical-imaging dissociation') in acute ischaemic stroke. *Cerebrovasc Dis* 2010;29:395-402.

5. Lovelock CE, Cordonnier C, Naka H, Al-Shahi Salman R, Sudlow CLM, The Edinburgh Stroke Study Group, Sorimachi T, Werring DJ, Gregoire SM, Imaizumi T, Lee S-H, Briely D, Rothwell PM. Antithrombotic drug use, cerebral microbleeds, and intracranial hemorrhage. A systematic review of published and unpublished studies. *Stroke* 2010;41:1222-1228.

6. Cordonnier C, Potter GM, Doubal F, Jackson CA, Keir S, Sudlow CLM, Wardlaw JM, Al-Shahi Salman R. Improving interrater agreement about brain microbleeds: development of the Brain Observer MicroBleed Scale (BOMBS). *Stroke* 2009;40:94-99.

Book chapters

1. Samarasekera N, Potter GM, Al-Shahi Salman R. Microbleed mimics. In Werring DJ, ed. *Cerebral Microbleeds: Pathophysiology to Clinical Practice*, 1st edition, Chapter 5, Cambridge University Press.

Submitted manuscripts

1. Potter GM, Doubal FN, Jackson CA, Sudlow CLM, Dennis MS, Wardlaw JM. Lack of an association between carotid artery stenosis and ipsilateral white matter lesions suggests emboli do not cause white matter lesions. Submitted to *J Neurol Neurosurg Psychiatry.*

2. Potter GM, Doubal FN, Jackson CA, Sudlow CLM, Dennis MS, Wardlaw JM. Are enlarged perivascular spaces associated with white matter hyperintensities and lacunar stroke? Submitted to *Eur Neurol*.

Published abstracts from conference presentations

1. Potter GM, Marlborough FJ, Wardlaw JM. Wide variation in reporting of lacunar-related lesions on imaging in lacunar stroke studies – literature review. (a) *Neuroradiology* 2010;52:421-440 (b) European Stroke Conference 2010, *Cerebrovasc Dis* 2010;29(Suppl 2).

2. Potter GM, Wardlaw JM. Wide variation in definitions, detection and description of lacunar lesions on imaging - an online survey of researchers in cerebral small vessel disease. European Stroke Conference 2010, *Cerebrovasc Dis* 2010;29(Suppl 2).

3. Potter GM, Doubal FN, Jackson CA, Sudlow CLM, Dennis MS, Wardlaw JM. White matter lesions identified by magnetic resonance imaging are not related to ipsilateral carotid artery stenosis so are unlikely to be embolic. (a) UK Stroke Forum 2007 http://tinyurl.com/yk82tmf (oral) (b) European Stroke Conference 2010, *Cerebrovasc Dis* 2010;(Suppl 2).

4. Potter GM, Doubal FN, Jackson CA, Chappell FM, Sudlow CLM, Dennis MS, Wardlaw JM. Long-term appearance of lacunar infarction on imaging: what proportion become CSF-containing cavities? (a) European Stroke Conference 2008, *Cerebrovasc Dis* 2008;25(Suppl 2) (oral) (b) UK Stroke Forum 2009 http://www.ukstrokeforum.org/events/past_forum_conferences/2009_conference.html (poster).

5. Potter GM, Doubal FN, Jackson CA, Sudlow CLM, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on brain MRI are associated with white matter hyperintensities and lacunar stroke (a) UK Stroke Forum 2008 http://www.ukstrokeforum.org/events/past_forum_conferences/2008_uksf_conference.html (oral).

6. Cordonnier C, Potter GM, Doubal F, Jackson CA, Keir S, Sudlow CLM, Wardlaw JM, Al-Shahi Salman R. Improving interrater agreement about brain microbleeds: development of the Brain Observer MicroBleed Scale (BOMBS). European Stroke Conference 2007, *Cerebrovasc Dis* 2007;23(Suppl 2) (poster, distinction awarded).

Conference presentations without published abstracts

1. Potter GM, Doubal FN, Jackson CA, Chappell FM, Sudlow CLM, Dennis MS, Wardlaw JM. Long-term appearance of lacunar infarction on imaging: what proportion become CSF-containing cavities? (a) Scottish Imaging Network: A Platform for Scientific Excellence (SINAPSE) Annual Meeting 2009 (oral) (b) British Society of Neuroradiologists Annual Meeting 2008 (poster prize awarded).

2. Potter GM, Doubal FN, Jackson CA, Sudlow CLM, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on brain MRI are associated with white matter hyperintensities and lacunar stroke. British Society of Neuroradiologists Annual Meeting 2008 (oral).

3. Potter GM, Doubal FN, Jackson CA, Sudlow CLM, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on brain MRI are associated with white matter hyperintensities and lacunar stroke. British Society of Neuroradiologists Annual Meeting 2008 (oral).

Abbreviations

BG	Basal ganglia
BG-EPVS	Basal ganglia enlarged perivascular spaces
BMB	Brain microbleeds
BOMBS	Brain Observer MicroBleed Scale
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CI	Confidence interval
CS	Centrum semiovale
CS-EPVS	Centrum semiovale enlarged perivascular spaces
CSF	Cerebrospinal fluid
CT	Computed tomography
DWI	Diffusion-weighted imaging
EPVS	Enlarged perivascular spaces
ESS	Edinburgh Stroke Study
FLAIR	Fluid attenuated inversion recovery
GRE	Gradient echo
LACS	Lacunar syndrome
MB	Midbrain
MB-EPVS	Midbrain enlarged perivascular spaces
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSS	Mild Stroke Study

NASCET	North American Symptomatic Carotid Endarterectomy Trial
NIHSS	National Institutes of Health Stroke Scale
OCSP	Oxford Community Stroke Project
OR	Odds ratio
PACS	Partial anterior circulation syndrome
POCS	Posterior circulation syndrome
PVS	Perivascular spaces
SD	Standard deviation
SVD	Small vessel disease
T1WI	T1-weighted imaging
T2WI	T2-weighted imaging
TACS	Total anterior circulation syndrome
TIA	Transient ischaemic attack
WMH	White matter hyperintensities
WML	White matter lesions

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Research strategies, image analysis, data extraction, data entry and statistical analysis

I co-designed imaging data collection forms with Professor Joanna Wardlaw. I analysed MR brain imaging from patients recruited to the Edinburgh Stroke Study and Mild Stroke Study. Fergal Marlborough, a medical student at the University of Edinburgh, assisted me with extracting data for work relating to reporting of lacunar lesions in the literature. Mrs. Sheila Kirk entered microbleed data into a database designed by Mr. Aidan Hutchison. I entered all other imaging data into Excel and Minitab, and I performed statistical analysis under the guidance of Dr. Steff Lewis, Dr. Francesca Chappell, Dr. Cat Graham and Dr. Fergus Doubal.

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Dedication

This thesis is dedicated to my parents, Maureen and Brian, and to my sister, Caroline, for their unfailing love and support.

Chapter 1. Introduction

1.1. The burden of stroke

Stroke is a major cause of death and disability. It is the third commonest cause of death worldwide after coronary heart disease and all cancers combined (Lopez et al. 2006), causing an estimated 5.7 million deaths in 2005, 87% of which were in low- and middle-income countries. Without intervention, the number of global deaths from stroke is predicted to rise to 6.5 million in 2015 and to 7.8 million in 2030 (Strong et al. 2007). Stroke is also a leading cause of disability (Lopez et al. 2006, Strong et al. 2007) and is the most important single cause of severe disability in people living in their own homes in the UK, costing the NHS and the economy approximately £7 billion per year, and accounting for about 6% of NHS and Social Services expenditure (Martin et al. 1988, National Audit Office 2005, Rothwell 2001).

1.2. Pathological types of stroke

Once stroke mimics (e.g. infection, neoplasm) have been excluded and a clinical diagnosis of stroke has been made, it is important to determine whether the stroke is due to cerebral ischaemia or haemorrhage. Approximately 80% of all strokes are due to cerebral ischaemia, and about a fifth to haemorrhage, which may be either parenchymal (15%) or subarachnoid (5%) in location (Feigin et al. 2003, Sudlow and Warlow 1997). The presence or absence of haemorrhage is most easily assessed on brain computed tomography (CT), although sensitivity for detection of haemorrhage may vary with stroke type and timing of imaging (Keir et al. 2002, Wardlaw et al. 2003a).

1.3. Classification of ischaemic stroke subtypes: large vs small vessel disease

In ischaemic stroke, the underlying cause is atherothromboembolic in approximately half of cases (originating in the extracranial neck vessels in most cases), cardiogenic emboli in 20% and small vessel disease (SVD) in approximately 25% (Warlow et al. 2003). Amongst the several classification systems currently used to categorise patients into large or small vessel disease (Amarenco et al. 2009), some use clinical assessment alone and are risk factor-free (Bamford et al. 1991), whilst others use a combination of clinical assessment, risk factors and investigations, and are therefore risk factor-based (Adams et al. 1993). Classification into ischaemic stroke subtypes helps guide patient management in day-to-day clinical practice but is also important for categorising patients in aetiological, epidemiological and pathophysiological studies.

1.4. The burden of lacunar stroke

Until recently, there has been relative neglect of small vessel lacunar stroke (once considered the most benign ischaemic stroke subtype), with attention having been mainly focussed on large artery cortical ischaemic stroke. This trend is reflected in the advances which have been made in therapeutic options for stroke, which are primarily concerned with large artery stroke. However, although the prognosis of small vessel stroke is more favourable (in terms of survival and disability) than large vessel ischaemic stroke during the first few years, in the long term, there is a greater risk of death, stroke recurrence, cognitive dysfunction and dementia than previously realised (Norrving 2003, Norrving 2008) and a similar loss of quality-adjusted life

expectancy compared to large artery stroke (Lee et al. 2010). Despite an increased focus on the causes and associations of cerebral small vessel disease in recent years, the exact mechanisms underlying lacunar stroke remain unclear, with proposed mechanisms including lipohyalinosis, arteriosclerosis, poor cerebral blood flow, vasospasm and abnormal endothelial function (Wardlaw et al. 2009). Acute treatment and secondary prevention of ischaemic stroke is therefore currently similar across all stroke subtypes.

1.5. Lacunar infarction

The term 'lacune' derives from the Latin *lacuna*, meaning a tiny hole, pit or cavity. The lacunar hypothesis suggests that symptomatic lacunar infarcts usually present with specific lacunar syndromes and usually are caused by a distinct vasculopathy of the small perforating arteries (Bamford and Warlow 1988; Figure 1). Five classic lacunar syndromes (pure motor hemiparesis, pure sensory stroke, sensorimotor stroke ataxic hemiparesis, dysarthria-clumsy hand syndrome and atypical lacunar syndrome; Boiten and Lodder 1991) have been described, although several other syndromes exist. Most of our current knowledge about lacunar infarction originates from the seminal clinicopathological studies of Miller Fisher in the 1950s and 1960s, who defined lacunes as 'infarcts caused by occlusion of small perforating arteries' (Fisher 1982). Neuropathological descriptions of lacunar lesions have subsequently been translated to imaging and defined as 'small, deep lesions measuring ≤20 mm (or ≤15 mm in some studies) located in the BG, thalamus, internal capsule, corona radiata and brainstem, resulting from occlusion of a single perforating artery' (Fisher 1991, Lammie 2000). However, clinicopathological studies in lacunar stroke are few in number due to the low early case fatality rate with most neuropathological

material being examined after clinical symptoms have occurred (Fisher 1969, Fisher 1979).

1.6. Imaging in stroke

In the 1970s, CT revolutionised brain imaging and made indirect imaging techniques, such as ventriculography, obsolete. The original EMI (Electric and Musical Industries Ltd.) scanner took 6 minutes to perform one slice and 20 minutes to reconstruct the image; with current multislice scanners, an unenhanced CT brain can be performed in only a few seconds and images reconstructed in minutes. Magnetic resonance imaging (MRI) was first used as a clinical tool in the early 1980s. A routine structural MR brain examination for stroke commonly consists of multiple sequences including T1- and either T2-weighted or fluid attenuated inversion recovery (FLAIR) imaging, diffusion-weighted imaging (DWI) and gradient echo (GRE, or T2*) imaging. For cooperative patients, this is normally performed in less than half an hour. Whilst MR is considered equivalent to CT for the detection of acute haemorrhage and superior to CT for the detection of ischaemia, CT remains the mainstay of routine imaging in patients presenting with possible stroke and is quick and easy to perform (Wardlaw et al. 2006). There are several constraints to MRI scanning in acute stroke, including the problem of restless and sick patients (Hand et al. 2005); however, those with mild stroke (lacunar or cortical) are more able to cooperate meaning a much larger proportion can be scanned (Wardlaw et al. 2003a). GRE and susceptibility-weighted MRI may be particularly useful in detecting haemorrhage in patients who present several days to weeks after symptom onset, when the distinguishing signs on CT will have gone.

The recent search for improvements in diagnostic and therapeutic strategies for patients with acute ischaemic stroke, and in particular large artery stroke, has been paralleled by rapid development in CT and MRI technology (Warach and Wardlaw et al. 2006) and it is now possible (using CT and/or MRI) to detect not only ischaemia and haemorrhage, but also vascular occlusion and 'tissue at risk' (ischaemic penumbra) in the same sitting by means of angiographic and perfusion techniques, respectively. The role of CT perfusion imaging in day-to-day clinical practice, particularly in terms of improved diagnostic accuracy (Lin et al. 2009, Wintermark et al. 2005), outcome prediction (Parsons et al. 2005), identification of penumbral tissue (Murphy et al. 2006, Wintermark et al. 2005) and thresholds of tissue viability (Bandera et al. 2006), has yet to be fully established, as have the roles of CT angiography (Ritter et al. 2006) and MR perfusion imaging (Kane et al. 2007, Ritter et al. 2006, Warach 2003).

In patients with suspected lacunar stroke, MRI is particularly useful compared to CT due to its greater sensitivity for detecting small lesions (Chalela et al. 2007; Figure 2); however, without DWI, many acute lacunar infarcts may not be detected, particularly in the presence of concomitant white matter lesions (WML).

1.7. The spectrum of cerebral small vessel disease

Lacunar infarction may be one manifestation of a spectrum of radiological markers of cerebral small vessel disease. Since the initial recognition of WML on cross sectional imaging, their aetiology, clinical associations and prognostic importance have been the focus of much research. WML are associated with increasing age, hypertension and lacunar stroke (Basile et al. 2006, De Leeuw et al. 2001, Fazekas et

al. 1988, Longstreth et al. 1996, Romero et al. 2009) and are also a marker of poor prognosis, particularly in terms of increased mortality and risk of dementia (Inzitari et al. 1997, Prins et al. 2004). Quantification of WML using visual and automated methods (Fazekas et al. 1987, Kappeller et al. 2003, Scheltens et al. 1993, Wahlund et al. 2001) has been central to their investigation.

Increasing use of MRI, including newer sequences such as GRE, or T2* imaging, has led to the increasing recognition of two other possible imaging markers of microangiopathy: enlarged perivascular spaces (EPVS) and brain microbleeds (BMB). EPVS (Virchow-Robin spaces) are cerebrospinal fluid (CSF)-filled cavities that surround the walls of vessels as they course from the subarachnoid space through the brain parenchyma (Kwee and Kwee 2007) and are best seen on T2-weighted imaging (T2WI) (Figure 3). EPVS are seen in normal individuals at all ages, but are found in increased numbers with age and have been associated with cerebral autosomal dominant arteriopathy with subcortical infarction and leukoencephalopathy (CADASIL; Cumurciuc et al. 2006), impaired cognitive function (MacLullich et al. 2004), dementia (Patankar et al. 2005), depression (Patankar et al. 2007), impaired cognition in diabetics (Ferguson et al. 2003), multiple sclerosis (Wuerfel et al. 2008) and more recently, with lacunar ischaemic stroke and WML (Doubal et al. 2010). BMB, first described in the mid-1990s (Chan et al. 1996, Greenberg et al. 1996, Offenbacher et al. 1996) and best seen on GRE sequences as small, homogeneous, round foci of hypointensity, are found in 5% of healthy adults, 34% of people with ischaemic stroke and 60% of those with non-traumatic intracerebral haemorrhage (Cordonnier et al. 2007; Figure 3). Extensive

studies are currently ongoing to determine the prognostic utility of BMB and whether or not they should influence treatment (Lovelock et al. 2010).

1.8. Unanswered questions

1.8.1. Clinical misclassification of lacunar stroke

Up to a fifth of lacunar infarcts are misdiagnosed as cortical infarcts clinically and vice versa (Potter et al. 2010a). The reasons for this are unclear, but there are important implications for categorising patients into aetiologic and prognostic subgroups in clinical practice and in studies of lacunar stroke. Research studies relying on clinical assessment alone to assign stroke subtype without radiological assessment – as is the case in large proportions of patients in epidemiological studies - may incorporate 'noise' from misclassification of lacunar stroke as cortical stroke and vice versa. The influence of lacunar infarct site, as well as other patient- and imaging-related factors, on stroke subtype misclassification, have not been assessed, but are important for further understanding of pathophysiology and avoidance of misclassification of lacunar stroke in other research.

1.8.2. Detection and definitions of lacunar-related lesions and the long-term appearances of symptomatic lacunar infarction

Despite the rapid accumulation of imaging studies of lacunar stroke since the introduction of cross sectional brain imaging, there remain uncertainties regarding the aetiology of lacunar infarction. Some of these uncertainties may have arisen from variation in lacunar lesion definitions and the imaging sequences used for diagnosis, as well as from difficulties in lacunar lesion detection, in part due to overlapping appearances of imaging markers of SVD. Lacunes, or CSF-containing cavities, are

often counted in epidemiological studies as old lacunar infarcts (Vermeer et al. 2007), but so far, the proportion of symptomatic lacunar infarcts progressing to lacunes has not been assessed; therefore many lacunes may be counted in error as lacunar infarcts and many true lacunar infarcts may never be counted if they do not cavitate. Clarification is required to make progress in understanding in lacunar disease.

1.8.3. The association between white matter lesions and carotid stenosis

As with lacunar stroke, the precise cause of WML is unclear. If lacunar stroke and associated features such as WML are primarily embolic in origin, more WML would be expected to occur distal to an embolic source such as a tight carotid stenosis. However, it is difficult to use lacunar stroke to look for an association with emboli because lacunar lesions are infrequent and several patients have more than one possible cause of stroke. Whilst several studies have assessed in various ways the relationship between carotid stenosis and WML, no studies have assessed the specific relationship between carotid stenosis asymmetry and asymmetric WML.

1.8.4. Associations of enlarged perivascular spaces

The pathophysiology and associations of EPVS are uncertain at present. They are not included in any classification of WML. Although several associations of EPVS are now beginning to emerge, the association between EPVS and lacunar stroke or WML has been addressed in only two previous studies (Adachi et al. 2000, Doubal et al. 2010). Progress is hampered by a lack of reliable methods of quantification, either by visual rating or by automated assessment.

1.8.5. Quantification of enlarged perivascular spaces and brain mircobleeds

Validated scales for assessing radiological features of cerebral SVD are important in helping to minimise interobserver variation, enable cross-comparison between studies, for use in analyses of associated clinical or other variables and to facilitate metaanalysis. Compared to the radiological assessment of WML, there is a relative lack of validated methods for quantifying both EPVS and BMB at present.

1.9. Aims of the thesis

Section one: Lacunar stroke and lacunar-related lesions

(1) To assess clinical and imaging features that might explain clinical misclassification of lacunar infarcts as cortical infarcts and vice versa, including the influence of lacunar lesion site.

(2) To assess the proportion of symptomatic lacunar infarcts which progress to cavities and to assess patient-related, stroke-related, and imaging-related associations of the cavitation process.

(3) To assess completeness of reporting of lacunar-related lesions in the lacunar stroke literature, including a range of related methodological features.

(4) To assess definitions and detection of lacunar-related lesions amongst researchers with an interest in cerebral SVD.

Section two: Associated features of cerebral small vessel disease

(5) To review the existing literature on the relationship between carotid stenosis and WML and to assess specifically the relationship between carotid stenosis and ipsilateral WML while controlling for the contralateral stenosis/WML.

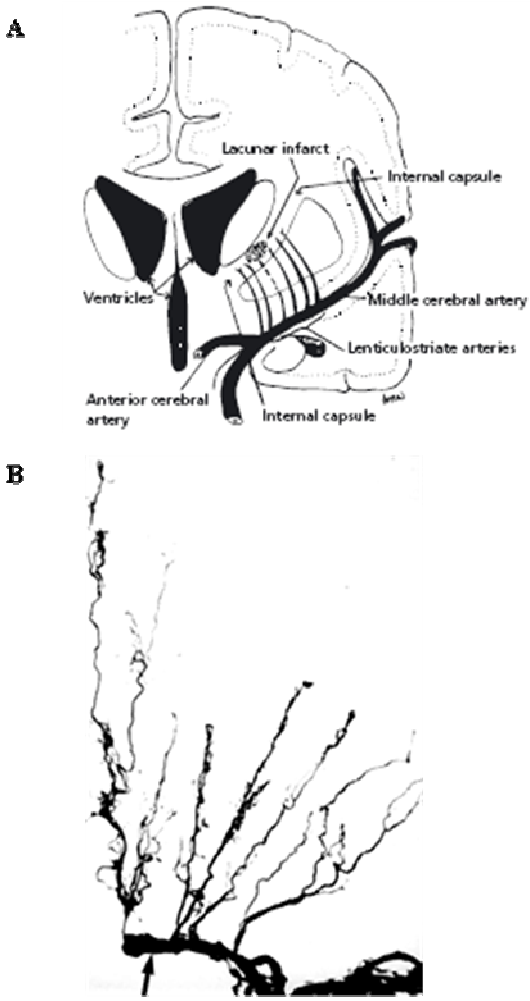
(6) To validate clinical and imaging associations of EPVS in a large, prospective ischaemic stroke cohort, including the association between EPVS and other features of cerebral SVD.

(7) To review existing methods for quantifying EPVS, to develop an improved visual EPVS rating scale, and to quantify intra- and interrater agreement in the assessment of EPVS on structural brain MRI.

(8) To develop a visual BMB rating scale and to quantify interrater agreement in the visual assessment of BMB.

1.10. Figures

Figure 1 (A) Diagrammatic representation of the likely vascular process underlying lacunar infarction. One of the lenticulostriate arteries is occluded (dashed line), causing an infarction in the internal capsule. (B) Post-mortem demonstration of the deep perforating (lenticulostriate) arteries arising from the main stem of the middle cerebral artery (arrow).



Reproduced from Warlow CP, van Gijn J, Dennis M, Wardlaw J, Bamford J, Hankey G, Sandercock P, Rinkel G, Langhorne P, Sudlow C, Rothwell P, eds. *Stroke: Practical Management,* 3rd edition, Chapter 4, pp146 & 148, by permission of Wiley InterScience.

Figure 2 MRI appearances of acute lacunar infarction

Axial MRI brain showing an acute lacunar infarct (arrows) in the left corona radiata on FLAIR (A), T2WI (B) and diffusion-weighted imaging (C). This lesion was hypointense on the corresponding apparent diffusion coefficient map (not shown). The block arrow indicates a probable enlarged perivascular space, with a surrounding FLAIR-hyperintense rim, adjacent to periventricular white matter lesions.

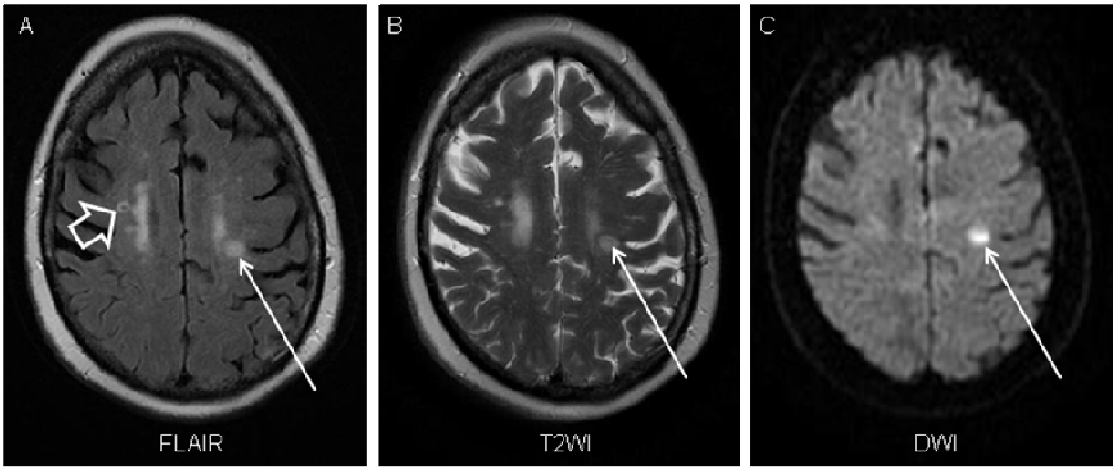
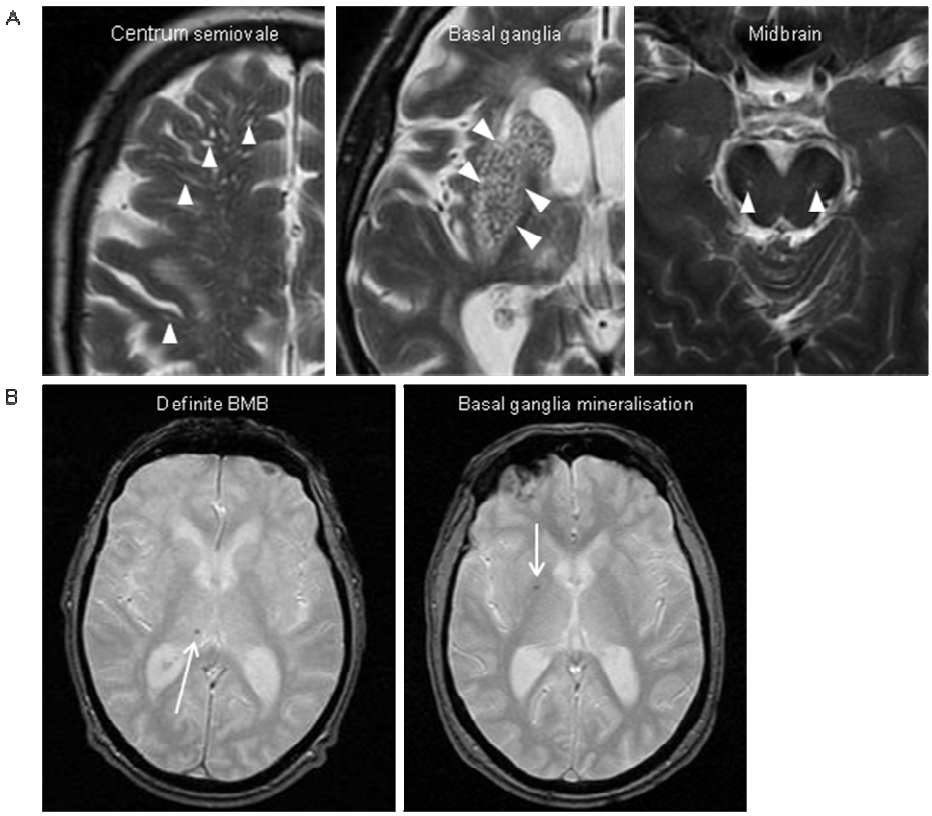


Figure 3 Axial brain MRI showing enlarged perivascular spaces (EPVS) and brain microbleeds (BMB)

(A) Magnified T2WI showing EPVS (arrowheads) in the three major anatomical locations: centrum semiovale, basal ganglia and midbrain. (B) Gradient echo imaging showing a 'true' microbleed in the right thalamus (arrow, left image). Solitary foci of hypointensity in the basal ganglia (arrow, right image), probably due to basal ganglia mineralisation, are common, and should be interpreted with caution.



Section one Neuroimaging of lacunar stroke

Chapter 2. Associations of clinical stroke misclassification ('clinical-imaging dissociation') in acute ischaemic stroke

2.1. Introduction

Classification of acute ischaemic stroke subtypes is important for categorising patients into aetiologic and prognostic subgroups in clinical trials, epidemiological and pathophysiological studies and may help guide patient management in clinical practice (Amarenco et al. 2009). Although it is well established that infarcts in particular locations are associated with specific neurological symptoms, clinical diagnosis of stroke lesion location may be difficult in the acute setting when the patient's neurological status may be unstable, meaning that a proportion of patients with acute ischaemic stroke will be incorrectly subtyped based on clinical assessment alone.

The Oxford Community Stroke Project (OCSP) clinical classification categorises patients based on clinical assessment alone into those with a lacunar syndrome (LACS), a partial anterior circulation syndrome (PACS), a total anterior circulation syndrome (TACS) or a posterior circulation syndrome (POCS) (Bamford et al. 1991). PACS and TACS both indicate cortical stroke syndromes. The OCSP classification can predict correctly the site and size of cerebral infarct, if visible, on CT or magnetic resonance (MR) brain imaging in about three quarters of patients (Mead et al. 2000). However, numerous studies demonstrate that about a fifth of patients with a cortical syndrome clinically have an acute lacunar infarct on imaging that accounts for their recent stroke symptoms; similarly some patients with a lacunar

syndrome clinically have an acute cortical infarct on brain imaging that accounts for their recent stroke symptoms (Al-Buhairi et al. 1998, Allder et al. 2003, Anderson et al. 1994, Ay et al. 1999, Kobayashi 2009, Lindgren et al. 2000, Lodder et al. 1994, Mead et al. 1999, Pittock et al. 2003, Seifert et al. 2005, Wessels et al. 2005, Wlodek et al. 2004), creating a 'clinical-imaging dissociation' (Table 2.2). This dissociation is important because epidemiological studies, primary treatment and secondary prevention trials in stroke have so far relied heavily on clinical classification so are likely to have incorporated 'noise' due to approximately one fifth of LACS and PACS patients being misclassified.

Several factors may contribute to clinical-imaging dissociation. Previous studies suggested that the side of brain affected by stroke (Mead et al. 2000), leukoaraiosis (Lodder et al. 1994), clinical severity (Allder et al. 2003, Lodder et al. 1994) and asymptomatic infarcts on imaging (Lodder et al. 1994) were associated with clinical-imaging dissociation. Other contributing factors have not been assessed. Delays in clinical assessment may allow neurological signs to resolve making an accurate history difficult to obtain (e.g. dysarthria and dysphasia can be difficult to distinguish on history alone); clinical examination may be insensitive to some subtle cortical signs (e.g. mild inattention) which would distinguish PACS from LACS. However the one previous study that examined delay to diagnosis did not find any association with clinical-imaging dissociation (Mead et al. 2000). Reliability of classification is affected by observer expertise in use of the OCSP classification, particularly in minor stroke (Selvarajah et al. 2009). Clinical-imaging dissociation may also arise when there is failure of brain imaging to ascertain relevant ischaemic lesions, either

because the imaging is relatively insensitive to small acute lesions (Chalela et al. 2007) or is performed too late to identify the acute lesion reliably.

2.2. Aims

Small subcortical infarcts are considered to cause their symptoms because their location in the subcortical white matter or BG effectively disconnects a larger section of cortex than is affected by an equivalent-sized lesion in the cortex (Figure 4). We hypothesised that a small subcortical infarct lying close to the cerebral cortex could mimic symptoms of a mild cortical syndrome (PACS) by causing functional disconnection of only a small area of cortex compared to one of the same size lying in the periventricular white matter or BG which would disconnect a larger area of cortex. We also considered that other factors, such as previous stroke, could increase the proportion with clinical-imaging dissociation, as residual features of a previous stroke could make interpretation of features due to the acute stroke difficult, and that common stroke risk factors might influence symptomatology.

2.3. Methods

2.3.1. Patient recruitment

We included patients from the Edinburgh Stroke Study (ESS), a prospectively-collected hospital-based stroke register of consecutive stroke and transient ischaemic attack (TIA) patients seen at a large academic teaching hospital between April 2002 and May 2005 (http://www.dcn.ed.ac.uk/ess/) (Jackson et al. 2009). In the present study we included only those patients who underwent MRI brain. We performed MR when time from stroke onset was greater than 5-7 days or uncertain, if there was

clinical uncertainty about the definite diagnosis of stroke (particularly in patients with prior stroke) or of the vascular territory involved (carotid or vertebrobasilar), if there was a potential underlying cause of stroke that required further investigation by advanced brain imaging, or if the patient was suitable for inclusion into other studies of large artery or subcortical stroke requiring brain MR. The ESS was approved by the Local Research Ethics Committee and all patients (or their relatives) gave written informed consent.

2.3.2. Clinical assessment

All patients were assessed by an experienced stroke physician who took a detailed history, performed a general and neurological examination and recorded the National Institutes of Health Stroke Scale (NIHSS) score (Appendices 1, 2). Patients were assigned a clinical subtype according to the OCSP classification based on the maximum stroke deficit. Lacunar and mild cortical syndromes (LACS and PACS, respectively) were defined according to the OCSP classification (Bamford et al. 1991). LACS was defined as one of the classical lacunar syndromes - i.e. pure motor weakness and/or sensory loss of face and arm, arm and leg or all three; or ataxic hemiparesis (ipsilateral corticospinal and cerebellar-like dysfunction without other features clearly localising to the posterior circulation, including dysarthria-clumsy hand syndrome and homolateral ataxia and crural paresis) - in the absence of visual field defect or higher cerebral dysfunction. In patients with faciobrachial or brachiocrural motor and/or sensory deficits, only involvement of the whole limb was considered acceptable for LACS; patients with involvement of less than the whole limb were classified as PACS. Mild cortical stroke syndrome (PACS) was defined as

a maximum clinical deficit of either: weakness or sensory loss in the face, arm or leg; loss of higher cerebral function (e.g. dysphasia or neglect); or weakness in more than one limb in the presence of loss of higher cerebral dysfunction or homonymous hemianopia. Isolated homonymous hemianopia was classified as a POCS (Bamford et al. 1991), a relatively crude grouping of posterior circulation cortical and lacunar lesions with clinical consequences which are generally less predictable because of the greater frequency of developmental vascular anomalies and greater variability of the territory supplied by individual arteries.

2.3.3. Investigations and assessment of risk factors

All patients had MRI including DWI, carotid Doppler ultrasound, electrocardiogram, blood tests and other investigations as indicated. We recorded risk factors including diabetes mellitus (defined as having a previous diagnosis of, or being on current medication for, diabetes), hypertension (defined as having a history of hypertension requiring medication) and prior history of stroke (i.e. clinical presentation with stroke).

2.3.4. Brain imaging

Patients underwent 1.5T MRI (GE Signa LX EchoSpeed scanner, Milwaukee, WI, USA). We collected sets of axial diffusion-weighted-echo planar images (sensitisation levels b=0 and 1000 s/mm^2) with diffusion gradients applied sequentially along 6 non-collinear directions (5 acquisitions including baseline T2WI-EP image and 6 diffusion-weighted echo planar images per slice position) with 5mm slice thickness, 1mm slice gap, 128 x 128 image matrix and 24 x 24 field

of view. Other MR parameters are shown in Table 2.1. Images were reviewed by a neuroradiologist (GMP), blinded to all clinical details.

2.3.5. Imaging classification

Location and size of recent infarcts were recorded (Appendix 1). Recent infarcts were defined as hyperintense on DWI, hypointense on the apparent diffusion coefficient map and either normal or hyperintense to normal brain on FLAIR/T2WI (less hyperintense than cerebrospinal fluid on T2). Lacunar infarcts were defined as round or ovoid lesions measuring ≤20mm in maximal diameter in the white matter, BG or brainstem. Proximity to cortex of recent lacunar infarcts was noted on any sequence on which the infarct was visible. We defined 'close to cortex' as the edge of the infarct lying within 2mm of the cortical margin in the white matter. Infarcts were defined as cortical where there was a typical configuration with involvement of cortex ± adjacent white matter, and striatocapsular where located in the BG or CS and measuring ≥20mm. Uncertain lesions were checked with a second neuroradiologist (JMW). A lacunar infarct was considered 'appropriate' in patients presenting with LACS; a lacunar infarct in the brainstem or thalamus, i.e. in the vertebrobasilar territory, was also considered 'appropriate' to a POCS. A small- or medium-sized cortical infarct was considered 'appropriate' in PACS. We also recorded white matter hyperintensities (WMH) (0-3 on the Fazekas scale (Fazekas et al. 1987); old strokes using all sequences; EPVS (defined as ≤2mm round or linear CSF-isointense lesions along the course of penetrating arteries, T2-hyperintense and T1/FLAIR-hypointense) in the BG and CS (0-4 on a local scale, where 0=none and

4=>40 (MacLullich et al. 2004); and atrophy (0-3 on a validated scale, where 0=none and 3=severe (Farrell et al. 2009).

2.3.6. Analysis

We assessed the statistical significance of differences in baseline characteristics and brain imaging features using Student's t-test for continuous variables, the Mann-Whitney test for non-normally distributed continuous variables and the χ^2 test for dichotomous variables. We performed multivariable analyses using logistic regression to determine independent factors for clinical-imaging dissociation. In the logistic regression model we included all variables from univariate analysis and obtained adjusted odds ratios (OR) (comparing patients with clinical-imaging dissociation versus those without) and 95% confidence intervals (CIs). We dichotomised scores for WMH (0-1 vs 2-3), brain tissue loss (0-1 vs 2-3) and EPVS (0-1 vs 2-4) due to low frequencies. We performed analyses using Minitab Statistical Software Version 15 (Minitab, Inc., State College, PA, USA).

2.4. Results

Amongst the 1311 acute ischaemic stroke patients recruited to the ESS, 313 underwent MR brain imaging, of whom 136 (43%) presented clinically with a PACS, 79 (25%) with a LACS, 24 (8%) with a TACS, 64 (21%) with a POCS and 10 (3%) with an uncertain OCSP classification (Figure 5). Ninety-three out of 136 (68%) patients with PACS and 44/79 (56%) patients with LACS had a diffusion-positive infarct relevant to the clinical presentation (Figure 5). Six (4%) patients with PACS and three (4%) LACS in whom DWI was normal had lesions on other sequences as the likely cause of symptoms. Patients undergoing MRI were slightly younger when

compared with the 1311 ischaemic stroke patients from which we identified our study population, with a higher proportion of males and a lower prevalence of diabetes but the proportion of PACS and LACS were similar (Table 2.2).

Sixty-nine (74%) patients presenting with a PACS had an acute cortical infarct (all small or medium-sized and considered appropriate to clinical syndrome) (Figure 5), 21 (23%) had an acute lacunar infarct (Figure 5) and three (3%) had a cerebellar infarct on DWI. Of patients presenting with a LACS, 37/44 (84%) had an acute lacunar infarct and seven (16%) had an acute cortical infarct. Most acute lacunar infarcts identified on DWI in patients presenting with a LACS or a PACS were located in the CS (18/37 LACS, 20/21 PACS). Amongst patients with an acute infarct on DWI, 65/138 (47%) patients had old infarcts on imaging, the median WMH score was 1.62 (range 0-3) and the median EPVS score was 2 (range 0-4).

In the cohort of 137 patients with PACS and LACS and an acute infarct on DWI, clinical-imaging dissociation was associated on univariate analysis with diabetes (p=0.001), increasing time from onset of stroke symptoms to MRI (p=0.05), EPVS (p=0.02) and old stroke lesions on brain imaging (p=0.02), but not with age (p=0.69), history of previous stroke (p=0.08), brain tissue loss (p=1.0) or WMH (0.12; Table 2.4). On multivariate analysis, diabetes (OR 7.12, 95% CI 1.86 to 27.2; p=0.004) was independently associated with clinical-imaging dissociation (Table 2.4).

Multiple acute infarcts were not associated with clinical-imaging dissociation either: amongst 44 LACS, five (11%) had multiple DWI-positive infarcts (all lacunar lesions) and none had clinical-imaging dissociation. Amongst 93 PACS, 15 (16%) had multiple DWI-positive infarcts, of whom two (13%) had clinical-imaging

dissociation (all multiple lacunar infarcts) and 13 (87%) were correctly associated (showing multiple cortical, or cortical plus cerebellar, infarcts; Figure 5).

We examined characteristics associated with a lacunar infarct causing a PACS clinical syndrome in all 72 patients with an acute lacunar infarct on DWI; 37 (51%) patients presented with LACS, 21 (29%) with PACS, and 14 (20%) with POCS (Table 2.5). Lacunar infarcts in POCS patients were located (appropriate to symptoms) in the posterior circulation territory (12 brainstem, 1 thalamus, 1 posterior borderzone) and were therefore not considered to have clinical-imaging dissociation. Clinical-imaging dissociation was associated in univariate analyses with increasing age (p=0.03), hypertension (0.004), increasing delay from symptom onset to clinical examination (p=0.001) and to MRI (p=0.04) and infarct positioned close to cortex (p=0.001) (Table 2.5). In multivariate analysis, closeness to cortex (OR 14.5, 95% CI 1.61 to 130.1; p=0.02) and older age (OR 1.16, 95% CI 1.0 to 1.30; p=0.01) remained independently associated with clinical-imaging dissociation; diabetes (OR 17.1, 95% CI 1.49 to 195.16; p=0.02) and left-hemispheric location (OR 8.95, 95% CI 1.23 to 64.99; p=0.03) were also independent associates (Table 2.5). There was no difference in the size of the lacunar infarcts between those causing PACS and those causing LACS clinical syndromes (mean 11.7 ± 3.4 versus 10.8 ± 4.3mm; p=0.32, nor in the size of those lacunar infarcts that were close to cortex and caused a PACS (n=16) or a LACS (n=15) (mean 12.3 ± 5.3mm versus 12 ± 3.7mm; p=0.8; Table 2.5).

2.5. Discussion

In our study of acute stroke patients with PACS and LACS and an acute infarct on DWI, we found that 23% of patients presenting with a PACS had an acute lacunar infarct, and 16% of patients presenting with a LACS had an acute cortical infarct and no other explanation for their recent stroke symptoms. The main factor associated with clinical-imaging dissociation amongst all patients in this study, after adjusting for potential confounders, was diabetes (old stroke lesions and previous history of stroke were associated in univariate analysis only) and in patients with an acute lacunar infarct on imaging, proximity of the lacunar infarct to the cortex, older age, diabetes and left hemisphere location. Lesion size, multiple acute infarcts, time to scanning, WMH, brain atrophy and history of prior stroke were not associated with clinical-imaging dissociation.

The present study had some methodologic strengths. We performed a more comprehensive examination of associated features than in previous studies of clinical-imaging dissociation. We identified consecutive stroke and TIA patients presenting to our stroke service. Patients undergoing MRI had similar proportions of PACS and LACS to the registry cohort as a whole. The minor differences between patients undergoing MRI and those that did not (slightly younger, more males, fewer with vascular risk factors) is unlikely to have influenced the generalisability of our results. All patients were very carefully examined by an experienced stroke physician and categorised according to strict interpretation of the OCSP criteria. Images were reviewed systematically according to a structured proforma by a trained rater using validated scales.

There were limitations in our study. Overall, only 313/1311 (24%) of patients presenting with acute stroke underwent MRI, which may have introduced a selection bias. Other factors which may have led to selection bias were the inclusion of patients with increasing delay, or uncertain time, since stroke onset, and where there was clinical uncertainty about stroke diagnosis. Our sample may therefore have included an overrepresentation of patients who were more difficult to subtype. However, this does not negate the observation that lacunar lesion location was associated with clinical-imaging dissociation. Median time from stroke onset to MRI was 19 days (many were out-patients, with mild stroke), i.e. outwith the time period generally considered optimal for DWI, and only 64% (137/215) patients had a diffusion-positive infarct. However, a previous small study showed no difference in the proportion with an acute infarct on DWI in those scanned before versus after four weeks (Schulz et al. 2003). Although several patients had DWI outwith the optimal time period, previous work has shown that DWI may also be useful up to several weeks after stroke onset (Keir et al. 2004). We also cannot exclude the possibility that the infarct responsible for initial symptoms was no longer visible on DWI by the time the patient underwent brain imaging, and that a new, silent DWI infarct (but sufficiently consistent with the infarct location as suggested by the symptoms and signs as to be considered as the acute index infarct) had appeared in this period, but this possibility was considered to be low and consequently not a significant confounding factor. We did not investigate underlying mechanisms as a cause of clinical-imaging dissociation, and the study was not designed to test the effect of clinician experience on misdiagnosis, a factor identified in one previous study (Selvarajah et al. 2009).

Previous studies did not consider proximity of lacunar infarcts to cortex or diabetes as possible factors for clinical-imaging dissociation. The association with diabetes may be partly explained by a co-association with old 'silent' infarcts; however, although old infarcts were associated with clinical-imaging dissociation in univariate analysis, they did not remain independently associated in multivariate analysis, as found previously (Lodder et al. 1994). Assigning clinical subtype may be more difficult in the presence of an old infarct, even if clinically silent, as signs from the previous infarct may confuse the clinical picture. The association of left hemisphere location and clinical-imaging dissociation is consistent with previous studies which found that left-sided lesions were more common in patients with PACS/non-lacunar syndrome with clinical-imaging dissociation (Lodder et al. 1994) and that right-sided lesions were more common in LACS presenting with clinical-imaging dissociation (Mead et al. 2000). This may be explained by the difficulty in distinguishing dysarthria from dysphasia, especially if symptoms and signs were mild or had resolved by the time of assessment. We did not find an association between clinical-imaging dissociation and WMH, in contrast to one previous study (Lodder et al. 1994), possibly because the latter used CT, which is less sensitive to WMH than MR FLAIR or T2.

We found that 11% of patients with LACS had multiple acute lacunar infarcts, similar to previous studies (Ay et al. 1999, Seifert et al. 2005, Wessels et al. 2005), but multiplicity of infarcts did not contribute to clinical-imaging dissociation. We did not find an association between time lapse from stroke onset to MRI and clinical-imaging dissociation, in agreement with one previous study using CT (Mead et al. 2000). Ability to recall symptoms and signs may deteriorate with increasing time to

assessment, particularly with speech disorders. Others have reported problems with very early or very late diagnosis of lacunar stroke (Toni et al. 1995). Our use of maximum deficit in assigning the OCSP subtype may have overcome any effect of time on clinical features, and so stroke diagnosis.

Clinical-imaging dissociation has important implications for research into the epidemiology, pathophysiology and treatment of lacunar stroke as well as for clinical practice. In research which relies heavily on clinical presentation alone, results may be affected by 'noise' caused by clinical-imaging dissociation in between 10% and 20% of patients with mild stroke. Studies in which CT is used in conjunction with clinical classification will also be affected, since CT is less sensitive than DWI for small acute infarcts (Chalela et al. 2007), particularly when performed soon after symptom onset, as is increasingly the case. Acute ischaemic stroke lesions are visible on CT in <20% of LACS and <35% PACS (i.e. mild stroke) at <3 hours, rising to approximately 45% and 60%, respectively, at 36 hours (Wardlaw et al. 2003b). The debate over mechanisms of lacunar stroke - up to 20% are said to be associated with cardiac and large artery atherothromboembolism (Futrell 2004, Kazui et al. 2001) rather than intrinsic SVD - could be explained by clinical-imaging dissociation. Similarly, large primary and secondary prevention trials of ischaemic stroke testing aspirin, cholesterol-lowering drugs and antihypertensives, have relied heavily on clinical classification and CT (CAPRIE Steering Committee 1996). ‘Noise’ from clinical-imaging dissociation may have impeded the demonstration of any difference in treatment effects between stroke subtypes, if one existed. In future, where precise diagnosis of stroke subtype and lesion location is important, lesion location should be verified by sensitive imaging.

2.6. Tables

Table 2.1 MRI scan parameters used in the Edinburgh Stroke Study and Mild Stroke Study

Sequence	TE	TR	Slice thickness (mm)	Slice gap (mm)	Matrix	Field of view	Flip angle
T2WI	102	6300	5	1.5	256 x 256	24 x 24	
T1WI	Min	450	5	1.5			
FLAIR	140	9000	5	1			
GRE	15	625	5	1.5	256 x 192	24 x 24	20^{o}

TE, time to echo; TR, time to repetition; T2WI, T2-weighted imaging; T1WI, T1-weighted imaging; FLAIR, fluid attenuated inversion recovery; GRE, gradient echo

Table 2.2 Previous studies identifying clinical-imaging dissociation and features examined

Study	Setting	Brain imaging	Stroke classification	Lacunar syndrome (N)	Lacunar syndrome + large subcortical or cortical infarct n (%)	Cortical syndrome (N)	Cortical syndrome + lacunar infarct n (%)	Features examined in relation to clinical-imaging dissociation
Lodder et al. 1994	Hospital	CT	-	147	23 (16)	203	19 (9)	Disability (OR 4.31, 95% CI 1.25-14.88) Leukoaraiosis (non-lacunar syndrome; OR 3.79, 95% CI 1.32-10.05) Asymptomatic infarcts (non-lacunar syndrome; OR 4.13, 95% CI 1.45-11.71) Hemisphere affected (non-lacunar syndrome)
Al-Buhairi et al. 1998	Hospital	CT	OCSP	-	-	121	4 (5)	-
Pittock et al. 2003	Hospital	CT	OCSP	47	2 (10)	24	3 (11)	-
Wlodek et al. 2004	Hospital	CT	OCSP	101	29 (29)	193	29 (15)	-
Kobayashi et al. 2009	Hospital	CT	OCSP	60	19 (31)	183	3 (2)	-
Mead et al. 1999	Hospital	CT, MRI	OCSP	180	35 (19)	395	62 (16)	-
Mead et al. 2000	Hospital	CT, MRI	OCSP	144	35 (24)	298	38 (13)	Hemisphere affected (PACS, LACS)
Anderson et al. 1994	Hospital, community	CT, MRI	OCSP	69	12 (17)	75	16 (21)	-

Table 2.2 continued

Study	Setting	Brain imaging	Stroke classification	Lacunar syndrome (N)	Lacunar syndrome + large subcortical or cortical infarct n (%)	Cortical syndrome (N)	Cortical syndrome + lacunar infarct n (%)	Features examined in relation to clinical-imaging dissociation
Ay et al. 1999	Hospital	DWI	-	62	1 (2)	-	-	-
Lindgren et al. 2000	Hospital	DWI	-	23	2 (9)	-	-	-
Allder et al. 2003	Hospital	DWI	OCSP	-	-	42	6 (14)	Clinical severity (χ^2 18.9, $p < 0.01$)
Seifert et al. 2005	Hospital	DWI	OCSP	-	-	93[a]	14 (15)	-
Wessels et al. 2005	Hospital	DWI	-	73	13 (18)[b]	-	-	-
This study	Hospital	DWI	OCSP	80	7 (16)	136	24 (25)	Old infarcts (OR 3.02, 95% CI 1.06 to 8.59) Diabetes (OR 7.17, 95% CI 1.86 to 27.71)

[a]Patients with subcortical or brainstem lesions <1.5cm in diameter

[b]4 with single cortical lesion, 9 with scattered or multiple lesions containing a cortical lesion

CT, computed tomography; OR, odds ratio; CI, confidence interval; OCSP, Oxford Community Stroke Project; MRI, magnetic resonance imaging; PACS, partial anterior circulation syndrome; LACS, lacunar syndrome; DWI, diffusion-weighted imaging

Table 2.3 Baseline characteristics of patients undergoing MRI compared to all acute ischaemic stroke patients recruited to the stroke register

	All acute ischaemic stroke patients (n=1311)	Patients with MRI (n=313)
Age in years (mean ± SD)	71.4 ± 12.9	68.5 ± 13.4
Male sex (%)	671 (51.2)	169 (54)
Risk factors		
Previous stroke	235 (18.0)	80 (25.6)
Hypertension	704 (53.7)	164 (53.1)
Diabetes	166 (12.7)	28 (9)
OCSP classification		
TACS	122 (9.3)	24 (7.7)
PACS	579 (44.2)	136 (43.4)
POCS	207 (15.8)	64 (20.5)
LACS	350 (26.7)	79 (25.2)
Uncertain	53 (4.0)	10 (3.2)

MRI, magnetic resonance imaging; SD, standard deviation; TACS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; LACS, lacunar syndrome

Table 2.4 Factors associated with clinical-imaging dissociation in patients with partial anterior circulation syndrome (PACS) and lacunar syndrome (LACS) and an acute infarct on magnetic resonance (MR) diffusion-weighted imaging

	Clinical-imaging dissociation (n=31)	No clinical-imaging dissociation (n=106)	Univariate statistic and test score	Univariate p value	Multivariate p value	Multivariate OR (95% CI)
Patient demographics						
Age (mean years ± SD)	71 ± 11	70 ± 13	Student's t-test -0.4	0.69	0.1	1.04 (0.98-1.10)†
Male gender	19 (61)	64 (60)	χ^2 0.008	0.93	0.74	1.21 (0.40-3.70)
Medical history						
Previous stroke n (%)	12 (39)	24 (23)	χ^2 3.03	0.08	0.14	2.38 (0.74-7.60)
Hypertension n (%)	23 (74)	58 (56)	χ^2 3.52	0.06	0.88	1.09 (0.36-3.34)
Diabetes n (%)	9 (29)	6 (6)	χ^2 11.2	0.001	0.004	7.12 (1.86-27.2)
Clinical						
Median days, onset to assessment	16	11	Mann Whitney 5 (0-12)		0.72	1.01 (0.96-1.07)
Range, (IQR)	0-97 (10-23)	0-125 (1-22)		0.09		
Median days, onset to MRI	21	15	Mann Whitney 8 (0-14)	0.05	0.71	1.01 (0.9-1.06)
Range (IQR)	0-97 (14-33)	0-140 (1-31)				
MR brain imaging characteristics						
Left hemisphere n (%)	17 (55)	61 (58)	χ^2 0.07	0.79	0.49	1.44 (0.51-4.09)
WMH 2-3[a] n (%)	16 (53)	39 (37)	χ^2 2.62	0.12	0.85	1.12 (0.35-3.55)
EPVS 2-4[b] n (%)	19 (63)	41 (340)	χ^2 5.2	0.02	0.38	1.61 (0.56-4.60)
Brain tissue loss 2-3[c] n (%)	8 (28)	29 (28)	χ^2 <0.001	1.0	0.1	0.33 (0.09-1.24)
Old stroke lesions n (%)	20 (65)	45 (42)	χ^2 5.49	0.02	0.08	2.56 (0.89-7.36)

†Odds ratio (OR) per additional year of age; [a]On Fazekas scale ; [b]On EPVS scale ; [c]On brain tissue loss scale; SD, standard deviation; CI, confidence interval; IQR, interquartile range; WMH, white matter hyperintensities; EPVS, enlarged perivascular spaces

Table 2.5 Associations with clinical-imaging dissociation in all subjects with an acute lacunar infarct on magnetic resonance (MR) diffusion-weighted imaging (n=72)

	Clinical-imaging dissociation (n=22)	No clinical-imaging dissociation (n=50)	Univariate statistic and test score	Univariate p value	Multivariate p value	Multivariate OR (95% CI)
Patient demographics						
Age (mean years ± SD)	75 ± 10	69 ± 11	t-test -2.33	0.03	0.01	1.16 (1.03-1.3(
Gender, male (%)	14 (64)	27 (54)	χ^2 0.58	0.45	0.09	5.25 (0.78-35.4
Medical history						
Previous stroke n (%)	6 (27)	8 (16)	χ^2 1.24	0.27	0.64	1.66 (0.20-13.
Hypertension n (%)	18 (82)	22 (44)	χ^2 8.85	0.004	0.12	3.72 (0.72-19.2
Diabetes n (%)	6 (27)	4 (8)	χ^2 4.75	0.06	0.02	17.1 (1.49-195.1
Clinical						
Median days, onset to assessment	18	14	Mann Whitney -6	0.04	0.49	1.05 (0.91-1.2
Range (IQR)	1-97 (14-23)	0-134 (3-22)				
Median days, onset to MRI	27	20	Mann Whitney -6	0.04	0.76	0.98 (0.84-1.1
Range, (IQR)	6-97 (16-32)	0-141 (6-29)				
MR brain imaging characteristics						
Subcortical infarct close to cortex n (%)	16 (73)	15 (30)	χ^2 11.4	0.001	0.02	14.5 (1.61-130
Infarct size (mm)	11.7 ± 3.4	10.8 ± 4.3	t-test -1.01	0.32	0.99	1.00 (0.82-1.2
Left hemisphere location n (%)	15 (68)	26 (52)	χ^2 1.22	0.27	0.03	8.95 (1.23-64.9
WMH 2-3[a] n (%)	12 (55)	20 (40)	χ^2 1.31	0.25	0.43	0.48 (0.08-2.9
EPVS 2-4[b] n (%)	14 (64)	25 (49)	χ^2 0.98	0.32	0.67	1.52 (0.22-10.4

Table 2.5 continued

	Clinical-imaging dissociation (n=22)	No clinical-imaging dissociation (n=50)	Univariate statistic and test score	Univariate p value	Multivariate p value	Multivariate OR (95% CI)
Brain tissue loss 2-3[c] n (%)	7 (32)	9 (18)	χ^2 1.69	0.19	0.35	0.30 (0.02-3.7
Old stroke lesions n (%)	14 (64)	23 (46)	χ^2 1.9	0.17	0.13	0.20 (0.02-1.6

†Odds ratio (OR) per additional year of age; [a]On Fazekas scale ; [b]On EPVS scale ; [c]On brain tissue loss scale ; OR, odds ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; WMH, white matter hyperintensities; EPVS, enlarged perivascular spaces

2.7. Figures

Figure 4 Coronal T1-weighted MRI brain to demonstrate how the site of a small subcortical (lacunar) infarct could influence clinical presentation

A small subcortical infarct lying in the left internal capsule, i.e. deep white matter (A), would cause functional disconnection of a large area of cortex (B, shaded). A peripheral small subcortical infarct lying close to cortex (C) would affect only a limited area of cortex (D, shaded), and could mimic a mild cortical stroke.

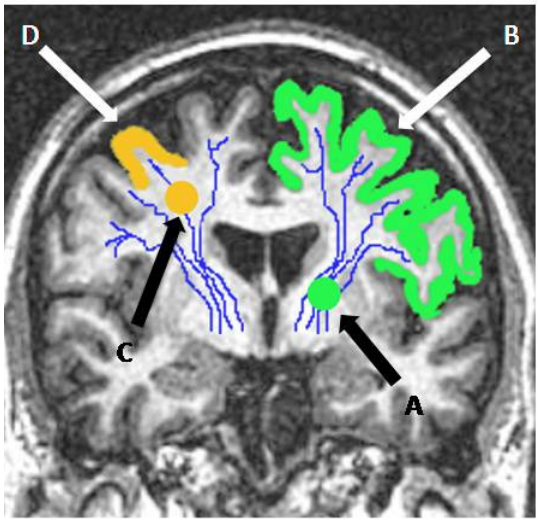
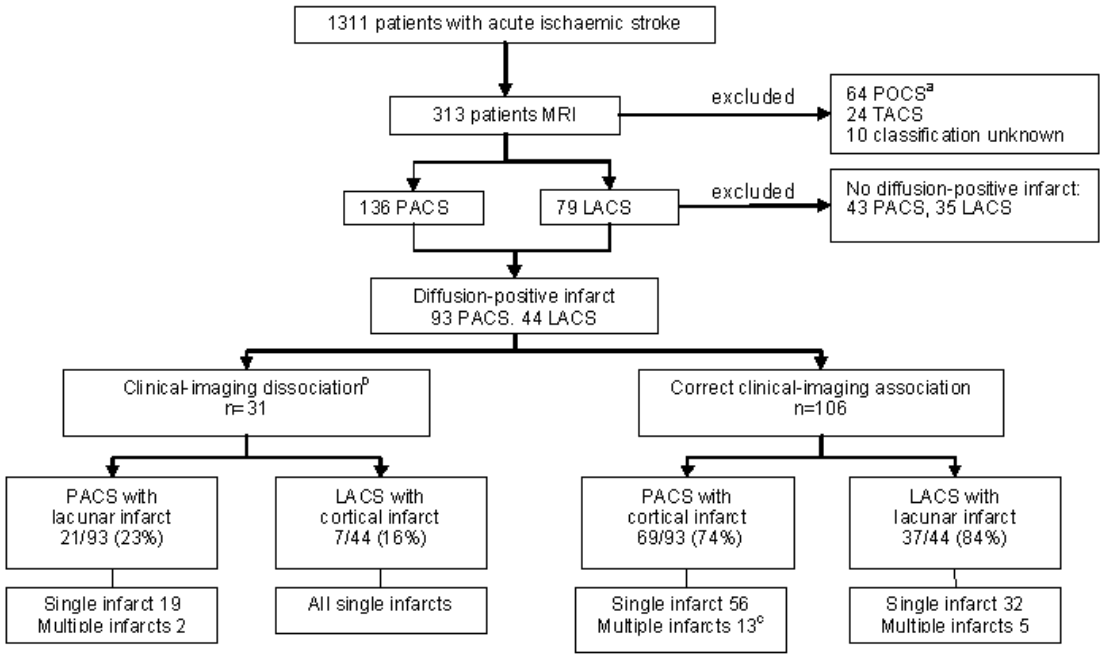


Figure 5 Identification of patients with partial anterior circulation syndrome (PACS) and lacunar syndrome (LACS) for assessment of clinical-imaging dissociation and imaging findings



MRI, magnetic resonance imaging; POCS, posterior circulation syndrome; TACS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; LACS, lacunar syndrome

[a]14 with acute lacunar infarct used in separate analysis (Table 2.5)

[b]3/93 (3%) with cerebellar infarct (not shown)

[c]11/13 multiple cortical infarcts, 2/13 cortical plus cerebellar infarct

Chapter 3. Counting cavitating lacunes underestimates the burden of lacunar infarction

3.1. Introduction

A lacune is commonly defined as a small, deep 3-20mm (or in some cases 3-15mm) CSF-containing cavity. The term 'lacune' was first used by Dechambre in 1838 (Dechambre 1838) and later in 1901 by Marie, who suggested these could be due to infarcts (Marie 1901). Sixty years later, Fisher defined lacunes pathologically as infarcts, either clinically silent or symptomatic, resulting from occlusion of a penetrating branch of a cerebral artery (Fisher 1965, Fisher 1969, Fisher 1982). The term 'lacune' is often used interchangeably with the terms 'lacunar infarct' and 'lacunar stroke'. Tissue loss replaced by CSF (or near-CSF) is also known radiologically as cerebromalacea, and can affect grey or white matter, but this term is usually applied to cortical infarcts.

Silent lacunes (on imaging or histopathology, without clear evidence of relevant stroke symptoms) are often termed 'silent lacunar infarcts' or 'silent brain infarcts'. Silent lacunes are frequently seen in healthy older people, occur in 8-28% of the general population, are associated with increasing age, hypertension and subtle deficits in physical and cognitive function, and more than double the risk of stroke and dementia (Vermeer et al. 2007). In most studies of 'silent brain infarcts', there is no definitive pathological evidence that the lesion was due to infarction.

3.2. Aims

The association between clinically evident lacunar ischaemic stroke and silent lacunes is unclear because the proportion in whom the symptomatic lacunar infarct progresses to a cavity, and in whom the lesion continues to resemble a WML, are unknown. This has significant implications for epidemiology (including risk factor) and pathogenesis studies of lacunar infarction and cerebral SVD, where it is common practice to count lacunes and only consider these as silent lacunar infarcts, omitting to correlate these with symptoms.

We investigated the proportion of symptomatic lacunar strokes progressing to lacunes, and assessed patient-related, stroke-related, and imaging-related associations of cavitation.

3.3. Methods

3.3.1. Patient recruitment

We identified patients with acute lacunar ischaemic stroke, diagnosed following clinical and radiological evaluation, with baseline and follow-up MR or CT brain imaging, from the ESS, a prospective register of consecutive stroke patients presenting to an academic teaching hospital (full details given in Chapter 2, 'Methods'), and the Mild Stroke Study (MSS; Appendix 4). In the MSS, patients with clinical lacunar or mild cortical stroke presented to our teaching hospital within three months of symptom onset between April 2005 and December 2007. Exclusion criteria were contraindications to MRI, unstable medical condition, and severe or haemorrhagic stroke.

3.3.2. Clinical assessment and assessment of risk factors

A stroke physician assigned a classification using the OCSP classification (Bamford et al. 1991), measured NIHSS score and assessed vascular risk factors. Written consent was obtained from all patients. Both studies were approved by the Local Research Ethics Committee.

3.3.3. Brain imaging

We included patients with baseline imaging with either brain MRI (including DWI, T2WI and FLAIR) or CT. We included patients with or without an acute lacunar infarct on MRI (because the high sensitivity of MR enabled us to exclude as fully as possible patients with cortical infarction), but on CT, only included patients with a visible recent lacunar infarct in the appropriate area for symptoms (because the low sensitivity of a negative CT would not allow us to exclude cortical stroke, which may give rise to lacunar-type symptoms) (Mead et al. 2000). Baseline and follow-up imaging was with either MR (including T1-weighted imaging (T1WI), T2WI, FLAIR and GRE sequences) or CT. Full MRI parameters are shown in Table 2.1 (ESS) and Table 3.1 (MSS). Patients with baseline diffusion-positive MRI and follow-up MRI were considered to represent a 'pure' subgroup, as diagnosis was most sensitive and specific for stroke subtype. The inclusion of the larger group in whom baseline imaging was either CT-positive or MR-negative enabled us to increase sample size, study power and generalisability.

3.3.4. Imaging classification

A neuroradiologist (GMP) recorded site and diameter of the acute index symptomatic lacunar infarct, WML, EPVS, cerebral atrophy, lacunes (separate from index lesion) and spongiform lesions (separate from index lesion). Acute lacunar infarcts were defined as round or ovoid lesions of increased signal relative to white matter on DWI, FLAIR or T2WI, or decreased attenuation relative to white matter on CT, 3-20mm in diameter, in the white matter, BG or brainstem. WML were rated on MRI (0-3 on Fazekas scale (Fazekas 1987) or CT (0-2 on van Swieten scale; van Swieten et al. 1990). EPVS, defined as ≤2mm round or linear CSF-isointense lesions along the course of penetrating arteries, were rated on MRI in the BG and CS (MacLullich et al. 2004) (0-4, where 0=none, 1=<10, 2=<20, 3=20-40 and 4=>40); atrophy was also rated (0-3 on validated scale (Farrell et al. 2009), where 0=none, 3=severe). Lacunes were defined as round or ovoid lesions of CSF attenuation/signal measuring 3-20mm in the white matter, BG or brainstem; correlation with appropriate symptoms was not sought. Coding was performed unblinded to clinical symptoms (to be certain of correct identification of the index lesion) but blind to all other clinical data.

At follow-up, a 'definite' cavity was defined as a lesion of CSF, or near-CSF, attenuation on CT, or of CSF signal on T2WI or FLAIR MRI, at the site of the index infarct (Figure 6). A 'possible' cavity was defined on FLAIR as a lesion of spongiform appearance with areas of marked hypointensity showing early confluence at the site of the index infarct. 'Definite' (CT and MRI) and 'possible' cavitation (FLAIR only) were considered together as 'any evidence of cavitation'. In cases of uncertainty, images were

reviewed by a second experienced neuroradiologist (JMW). Lacunes developing elsewhere in the brain between baseline and follow-up imaging were also recorded; correlation with appropriate symptoms was not sought for these lesions.

3.3.5. Analysis

We calculated proportions with any evidence of, and definite, cavitation (with 95% CIs) in the whole group, the 'pure' subgroup and the subgroup with an index infarct. We assessed statistical significance of differences in baseline characteristics and imaging features in patients with 'definite' and 'any' ('definite' plus 'possible') cavitation of the index lacunar infarct in the whole group and 'pure' subgroup. We used the Student's t-test for continuous variables, the Mann-Whitney-U test for non-normally distributed continuous variables and the $\chi 2$ test for dichotomous variables. We performed multivariate analysis using logistic regression to determine independent predictors of cavitation, allowing one variable per five outcome events. We obtained adjusted OR and 95% CIs, comparing patients with 'any' and 'definite' cavitation versus those without. For 'any evidence of cavitation', we used significant variables from univariate analysis (hypertension, diabetes, time to follow-up), and concomitant lacunes at baseline and deep atrophy, considered more likely than other features to be associated with cavitation. For 'definite' cavitation, we included time to follow-up (significant on univariate analysis), hypertension (significant in univariate analysis for 'any evidence' of cavitation'), and deep atrophy. We dichotomised scores for WML (Fazekas 0-1 vs 2-3, Fazekas 1987; van Swieten 0 vs 1-2, van Swieten et al. 1990), brain tissue loss (Farrell et al. 2009) and EPVS (0-2 vs 3-4) due to low frequencies. We also examined the

proportion with any progression of cavitation of existing 'spongiform' non-index lesions. All statistical analyses were carried out Minitab Statistical Software Version 15 (Minitab, Inc., State College, PA, USA).

3.4. Results

Ninety patients met our inclusion criteria. Mean age was 67±12 years, 48 (53%) had a history of hypertension, 18 (20%) diabetes and 12 (13%) a history of previous stroke. A 'pure' subgroup of 47/90 (52%) patients had a DWI-positive acute lacunar infarct and follow-up MRI (Table 3.2); six had baseline MR and follow-up CT; and 21 had baseline CT with either CT or MR follow-up.

Of the 74/90 (82%) patients with an acute index lacunar infarct, 45/74 (60%) were in the CS, 18/74 (24%) in the internal capsule, 9/74 (12%) in the thalamus and 3/74 (4%) in the brainstem. Of the 16/90 MRI-negative patients, follow-up MRI was normal in 15, and showed a non-cavitating lesion in an appropriate site for original symptoms in one (Table 3.2).

On follow-up imaging, 18/90 (20%, 95% CI 12 to 28%) patients showed 'definite', and a further seven 'possible', cavitation, making a total of 25/90 (28%, 95% CI 19 to 37%) with 'any evidence of' cavitation (Table 3.2). In the 'pure' subgroup, 7/47 (18%) had 'definite' cavitation and a further seven showed 'possible' cavitation, making a total of 14/47 with 'any evidence of 'cavitation (30%, 95% CI 17 to 43%). In sensitivity analyses to exclude patients without a DWI-positive lesion at baseline (i.e. 74 patients with visible lacunar infarction), 'definite' cavitation was visible in 18 (24%, 95% CI 15

to 34%) and ‘possible’ cavitation in a further seven; therefore 25/74 (34%, 95% CI 23 to 45%) showed ‘any evidence of’ cavitation. In one case, an acute lacunar infarct on baseline CT was not visible on follow-up MRI.

In the entire group of 90 patients, cavitation was associated with increasing time to follow-up imaging in those with both ‘definite’ and ‘any’ evidence of cavitation on univariate analysis (p=0.0003 and p=0.03, respectively, Tables 3.3 and 3.4); and with deep atrophy in patients with ‘definite’ cavitation (p=0.03). Figure 7 shows the time from stroke onset to follow-up imaging in patients with ‘definite’ cavitation. In patients with ‘any evidence of’ cavitation, hypertension and diabetes were negatively associated with cavitation (p=0.01 and 0.02, respectively). In multivariate analysis, increasing time to follow-up and deep atrophy remained significant for patients with ‘definite’ cavitation (OR 1.81, 95% CI 1.12 to 2.92% and OR 3.24, 95% CI 1.02 to 10.27%). No other patient-related, stroke-related or imaging-related variables (age, NIHSS and all other features of SVD) were associated with ‘any evidence of’, or ‘definite’, cavitation.

In the subgroup of 47 patients with a positive baseline diffusion scan and follow-up MRI, ‘definite’ cavitation was associated on univariate analysis with increasing time to follow-up (p=0.009) and superficial atrophy (p=0.03). In those with ‘any’ evidence of cavitation, hypertension was negatively associated with cavitation (p=0.009). No other clinical or imaging features were associated with cavitation in either the whole group or ‘pure’ subgroup.

At baseline, 13/90 patients (14%) had subcortical spongiform lesions separate from the index acute lacunar infarct (single lesion in 10, two lesions in 3). Progression to a 'definite' cavity on follow-up occurred in two of these patients, but in neither patient did the index lesion show 'any evidence of' cavitation; from the 11 spongiform lesions which did not progress to a 'definite' cavity, the index lacunar infarct showed progression to a 'definite' cavity in two patients.

At baseline, 31/90 (34%) patients had concomitant lacunes. Of these, 18/31 (58%) had higher WML scores, than the 17/59 (29%) without concomitant lacunes at baseline (χ^2 p=0.007); 4/31 (4%) patients developed new lacunes between baseline and follow-up imaging (unrelated to the index lesion) over an interval ranging from 76 to 185 days.

3.5. Discussion

The proportion of symptomatic lacunar infarcts which undergo cavitation to lacunes is unknown. In this study, a fifth of patients with acute lacunar ischaemic stroke showed 'definite' cavitation on follow-up imaging at a median of 227 days (range 54-1722) after stroke onset. In a 'pure' subgroup (DWI-positive infarct with follow-up MRI), 15% of patients showed 'definite' cavitation. 'Definite' cavitation was associated with increasing time to follow-up in univariate and multivariate analysis, but not with age, NIHSS, lesion size or location, or other features of cerebral SVD, including other lacunes. The association with increasing time to follow-up remained significant in the 'pure' subgroup. If these proportions are similar in other populations, up to 4/5 of

symptomatic lacunar infarcts may resemble, and be misidentified as, WML at any time up to approximately five years after stroke, possibly longer.

'Definite' cavitation was associated with deep atrophy in univariate and multivariate analysis and with superficial atrophy in the 'pure' subgroup. Our data indicate that age, stroke severity, and other features of SVD (WML, concomitant lacunes and EPVS) were not linked to cavitation. On the other hand, hypertension was negatively associated with cavitation in patients with 'any evidence of' cavitation (in both the whole group and 'pure' subgroup) and diabetes in the whole group.

The main strengths of our study were that patients were carefully characterised clinically to be certain of the clinical diagnosis of lacunar stroke, all data were collected according to pre-specified criteria, and most patients had baseline MRI, including diffusion. Thus, we could pinpoint precisely when the index lesion started and follow its evolution with precision. The two studies from which these data are derived were performed prospectively in the same hospital, using the same data collection, case ascertainment, diagnostic methods, physicians, radiologists and imaging equipment. We tested associations in the whole, as well as 'pure', subgroup, and found that they were similar.

Potential limitations were inclusion of a small proportion of patients without a lesion on MRI at baseline; some patients with non-lacunar stroke may have been inadvertently included, despite careful clinical characterisation. This may have meant we underestimated the proportion of patients with cavitation. However, after excluding MRI-negative patients, proportions with 'any evidence of' and 'definite' cavitation were

similar to the whole group, and to the 'pure' subgroup, with overall point estimates around 15% to 33%.

Minimum time to follow-up imaging was relatively short, but several patients without 'definite' cavitation had follow-up imaging at almost four years, and we identified patients with 'definite' cavitation at 54 days. Sample size was relatively small and precluded more complex analyses, so we cannot exclude weak associations between cavitation and imaging-, stroke-, or patient-related features. We were unable to investigate the influence of some factors, e.g. duration of symptoms or contrast enhancement, as this information was not collected. Follow-up timing was not fixed with variable times to follow-up; in the study of lacunar stroke, follow-up was at between one and three months and all patients were recalled for imaging (although not all attended), whereas in the stroke registry, follow-up mostly occurred if the patient developed new symptoms. These selection criteria in the original studies may have influenced cavitation detection rates. Larger studies with fixed follow-up time points are required to obtain more precise data on cavitation.

No previous studies have examined cavitation rates in symptomatic lacunar ischaemic stroke, so there is little information with which to draw comparisons. Longitudinal studies show that WML and lacunes increase in number over time, with hypertension (amongst others) being a risk factor for new lacunes, and diabetes and hypertension being risk factors (amongst others) for WML progression (Basile 2006, Gouw et al. 2008). We found that increased WML severity was associated with concomitant lacunes on baseline imaging, in agreement with previous studies (Mantyla et al. 1999, Vermeer

et al. 2003). Gouw et al. (Gouw et al. 2008) found that WML progression was modestly correlated with number of new lacunes at follow-up; we were unable to investigate for such a correlation. The apparent co-association of lacunes and WML suggests that lacunes may represent the extreme end of a spectrum of small vessel changes.

Factors associated with cavitation have been investigated in multiple sclerosis (MS); in longitudinal studies, a ring-enhancing lesion pattern is associated with cavity development (Bagnato et al. 2003, Minneboo et al. 2005, van Waesberghe et al. 1998, Zivadinov and Zorzon 2002), but predictive power is limited because of variability in cavity development, with some evidence that cavitation is patient-specific. Differences in MS lesion evolution in the same patient have also been demonstrated, suggesting local inflammatory reaction or location may be more relevant than individual susceptibility in leading to permanent axonal loss (Ciccarelli et al. 1999). Duration of symptoms may influence whether cavitation occurs (we did not record this), although we found no association with NIHSS, another marker of stroke severity. In animals, duration of middle cerebral artery occlusion has been shown to influence infarct cavitation (Garcia et al. 1997).

The molecular processes underlying cerebral tissue damage and repair, through the stages of tissue infarction and ‘rarefaction’, leading to gliosis and cavitation, are complex, and as yet incompletely identified (del Zoppo 2009). Histologically, a phase of chronic inflammation, including cavitation, was identified from 10 days to 53 years in patients with cortical and lacunar infarction (Mena et al. 2004). In our study, the earliest time at which a lesion demonstrated ‘any evidence of’ cavitation was 39 days, and at 54

days for ‘definite cavitation’. Matrix metalloproteinases are important factors for tissue remodelling implicated in all main cerebrovascular diseases including ischaemia and white matter lesions in vascular dementia (Rosenberg et al. 2001). Higher levels of matrix metalloproteinase (MMP-9) may be related to neurological deterioration in the first seven days after acute lacunar infarction, but there is no information on whether high MMP levels are associated with cavitation (Kim et al. 2006).

Thirteen patients in our study had spongiform lesions (possible cavities) separate to the index lesion at baseline; in two patients these progressed to definite cavities, but the index lesion showed no cavitation. Similarly, two patients with definite cavitation of the index lesion showed no progression to cavitation in non-index spongiform lesions. Cavitation may therefore occur on a ‘per lesion’ rather than ‘per patient’ basis.

What are the implications if only 1/5 of acute symptomatic lacunar infarcts become cavities and the other 4/5 continue to resemble WML? In epidemiology (including risk factor) and pathophysiology studies of lacunar infarction which only count lacunes as old lacunar infarcts, the true burden of lacunar disease may be underestimated by as much as five times. With the difficulties in distinguishing between WML and non-cavitated lacunar infarction, consideration should be given to abandoning the term ‘white matter lesions’ in favour of a term such as ‘small vessel changes’, correlating acute lacunar infarcts, ‘WML’ and lacunes with symptoms wherever possible. Our findings should be confirmed in larger prospective studies of acute lacunar stroke, with follow-up at pre-specified time intervals.

3.6. Tables

Table 3.1 MRI scan parameters used in the Mild Stroke Study

Sequence	TE	TR	Slice thickness (mm)	Slice gap (mm)	Matrix	Field of view	Flip angle
T2WI	102	6300	5	1.5	256 x 256	24 x 24	
T1WI	Min	450	5	1.5			
FLAIR	140	9000	5	1			
GRE	15	625	5	1.5	256 x 192	24 x 24	20^{o}

TE, time to echo; TR, time to repetition; T2WI, T2-weighted imaging; T1WI, T1-weighted imaging; FLAIR, fluid attenuated inversion recovery; GRE, gradient echo

Table 3.2 Type of brain imaging, including follow-up appearance of symptomatic lacunar infarct (n=90)

Type of imaging				Infarct visible at follow-up		Cavitation at follow-up		
Baseline	Follow-up	DWI - positive	n	Yes	No	None	Possible	Definite
MR	MR	Yes	47[a]	47	0	33	7	7
MR	CT	Yes	6	6	0	4	NA	2
MR	MR	No	16	1	16	1	0	0
CT	MR	NA	10	9	1	6	0	3
CT	CT	NA	11	11	0	5	NA	6

[a]'Pure' subgroup; DWI, diffusion-weighted imaging; MR, magnetic resonance; CT, computed tomography; NA, not applicable

Table 3.3 Clinical and imaging associations of lacunar infarct cavitation in patients with any evidence of cavitation (n=90)

	n where not 90	Any evidence of cavitation		Test	p value
		Yes (n=25)	No (n=65)		
Age in years (mean ± SD)		68.3 ± 12.3	66.8 ± 12	t test	0.59
Male (%)		16 (64)	38 (58)	χ^2	0.81
NIHSS median score (range)	86	1 (0-11)	2 (0-9)	Mann-Whitney	0.66
Stroke (%)		1 (4)	11 (17)	Fisher's	0.17
Hypertension (%)		8 (32)	40 (62)	χ^2	0.01
Diabetes (%)		1 (4)	17 (26)	Fisher's	0.02
Onset to assessment, median days (range)		16 (0-43)	9 (0-104)	Mann-Whitney	0.56
Onset to baseline imaging, median days (range)		17 (0-43)	9 (0-104)	Mann-Whitney	0.44
Onset to follow-up imaging, median days (range)		102 (39-1722)	74 (6-1440)	Mann-Whitney	0.03
Lacunar size mm (mean ± SD)	74	9.9 ± 3.2	9.7 ± 4.2	t test	0.87
Other lacunes baseline		9 (36)	22 (34)	χ^2	0.85
Deep WML[a] (0:1 vs 2:3)	80	7 (27)	24 (39)	χ^2	0.85

Table 3.3 continued

Periventricular WML[a] (0:1 vs 2:3)	80	13 (68)	35 (57)	χ^2	0.39
Anterior WML[b] (0 v 1:2)	10	3 (50)	3 (75)	Fisher's	0.57
Posterior WML[b] (0 v 1:2)	10	1 (17)	2 (50)	Fisher's	0.5
Deep atrophy (0:1 vs 2:3)		11 (44)	24 (37)	χ^2	0.54
Superficial atrophy (0:1 vs 2:3)		5 (20)	11 (17)	χ^2	0.74
Basal ganglia EPVS (0:2 vs 3:4)	80	3 (16)	18 (30)	Fisher's	0.37
Centrum semiovale EPVS (0:2 vs 3:4)	80	8 (42)	22 (36)	χ^2	0.64

[a]Fazekas scale; [b]van Swieten scale

SD, standard deviation; NIHSS, National Institutes for Health Stroke Scale; WML, white matter lesions; EPVS, enlarged perivascular spaces

Table 3.4 Clinical and imaging associations of lacunar infarct cavitation in patients with definite cavitation (n=90)

	n where not 90	Definite cavitation			
		Yes (n=18)	No (n=72)	Test	p value
Age in years (mean ± SD)		69.6 ± 11.1	66.6 ± 12.3	t test	0.33
Male (%)		13 (72)	41 (57)	χ^2	0.23
NIHSS median score (range)	86	2 (0-11)	1 (0-9)	Mann-Whitney	0.61
Stroke (%)		1 (6)	11 (15)	Fisher's	0.45
Hypertension (%)		6 (33)	42 (58)	χ^2	0.056
Diabetes (%)		1 (6)	17 (24)	Fisher's	0.11
Onset to assessment, median days (range)		17 (0-43)	9 (0-104)	Mann-Whitney	0.43
Onset to baseline imaging, median days (range)		18 (0-43)	10 (0-104)	Mann-Whitney	0.49
Onset to follow-up imaging, median days (range)		227 (54-1722)	72 (6-1440)	Mann-Whitney	0.0003
Lacunar size mm (mean ± SD)	74	9.28 ± 2.82	9.95 ± 4.14	t test	0.44
Other lacunes at baseline		6 (33)	25 (35)	χ^2	0.91

Table 3.4 continued

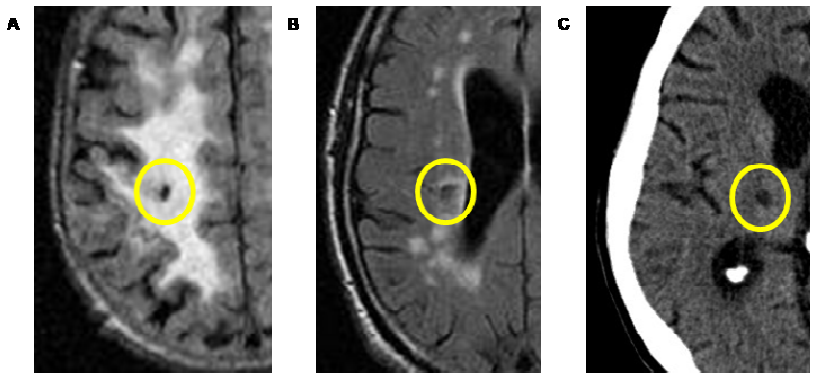
Deep WML[a] (0:1 vs 2:3)	80	4 (39)	27 (40)		0.76
Periventricular WML[a] (0:1 vs 2:3)	80	8 (67)	40 (59)	Fisher's	0.75
Anterior WML[b] (0 vs 1:2)	10	3 (50)	3 (75)	Fisher's	0.57
		Definite cavitation			
	n where not 90	Yes (n=18)	No (n=72)	Test	p value
Posterior WML[b] (0 vs 1:2)	10	1 (17)	2 (50)	Fisher's	0.5
Deep atrophy (0:1 vs 2:3)		11 (61)	24 (33)	Chi squared	0.03
Superficial atrophy (0:1 vs 2:3)		5 (28)	11 (15)	Chi squared	0.24
Basal ganglia EPVS (0:2 vs 3:4)	80	3 (25)	3 (25)	18 (26)	1
Centrum semiovale EPVS (0:2 vs 3:4)	80	5 (42)	25 (37)	Chi squared	0.75

[a]Fazekas scale; [b]van Swieten scale;
SD, standard deviation; NIHSS, National Institutes for Health Stroke Scale; WML, white matter lesions; EPVS, enlarged perivascular spaces

3.7. Figures

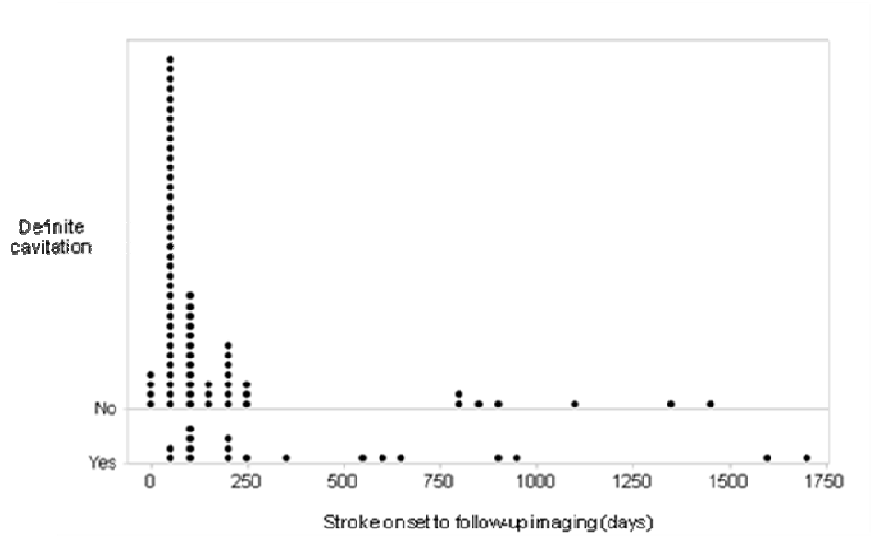
Figure 6 Examples of definite and possible lacunar infarction cavitation on MRI and a cavitated lesion on CT

Definite (A) and possible (B) cavities in the centrum semiovale on FLAIR MRI, both with concomitant white matter lesions (not labelled). C. Cavity in the right thalamus on CT.



FLAIR MRI, fluid-attenuated inversion recovery magnetic resonance imaging; CT, computed tomography

Figure 7 Time to follow-up imaging in patients with and without definite cavitation



Chapter 4. Wide variation in reporting of lacunar-related lesions on imaging in lacunar stroke studies – literature review

4.1. Introduction

Lacunar stroke accounts for about 25% of ischaemic stroke (Bamford et al. 1991). On brain imaging, lacunar lesions form part of a spectrum of features of cerebral SVD, which includes WML, EPVS and microbleeds. Several terms used for lacunar lesions found on imaging (e.g. 'lacunar infarct', 'lacunar stroke', 'lacune') appear to be used interchangeably (Wardlaw 2008). Non-specific and interchangeable use of terms for lacunar lesions on imaging may be contributing to the current debate on causes of lacunar stroke (Davis and Donnan 2004, Futrell 2004, Norrving 2004). Variations in clinical, neuropathological, and radiological terminology and definitions have complicated research in other related areas such as vascular dementia (Chui et al. 2000, Erkinjuntti et al. 1997, Leys and Pasquier 1998, Pantoni et al. 2006, Pohjasvaara et al. 2000, Román et al. 1993, Skinner et al. 2000, van Straaten et al. 2003). Ways of reducing heterogeneity by providing standardised classification systems for the imaging assessment of other radiological features of SVD - WML (Pantoni et al. 2002) and BMB (Cordonnier 2009) - have been addressed, but the consistency of imaging assessment in lacunar stroke has not been addressed. Therefore the literature was surveyed to quantify the range and variation of imaging definitions of acute and old lacunar stroke lesions and related methodological features.

4.2. Aims

In this study, we assessed reporting of imaging definitions of acute and old lacunar stroke lesions in the lacunar stroke literature, including a range of related methodological features.

4.3. Methods

We searched PubMed for articles between 1998-2008 in three journals with a focus on stroke (Stroke, Cerebrovascular Diseases and the Journal of Neurology), using the terms 'lacunar', 'lacune' and 'subcortical'. We performed initial testing of the data collection form on 10 articles before assessing a further 50 articles describing lacunar stroke studies in patients. We had intended to sample more, but as marked diversity was apparent in the first 50, we did not assess any further articles. Articles were selected from each journal at random using a random number generator. Data extraction was done by two observers (GMP, FJM), with data cross-checked by GMP. A third author arbitrated on any disagreements. Articles describing animal studies were excluded. Where there were two or more articles by the same authors, we used the methodology from only one article to avoid duplication of data.

We collected data on corresponding author and inclusion of a general radiologist or neuroradiologist in the authorship (Appendix 5). For acute and old lacunar lesions we collected details as shown in Table 4.1. We also collected imaging-related data about discipline, number, blinding and experience of those interpreting images.

4.3.1. Analysis

We assessed the proportion of articles providing clinical and imaging definitions, the imaging modality used, the discipline of corresponding author and the number of papers with a radiologist in the authorship. We listed all terms used to describe lacunar lesions on imaging and the proportion using each. We determined proportions (1) describing lesion size, site, attenuation/intensity and clinical terminology, (2) providing details about timing of imaging in relation to acute stroke symptoms, (3) attempting to relate old lacunar lesions to symptoms, and (4) attempting to differentiate old lacunar lesions from EPVS.

4.4. Results

4.4.1. Article type, authorship and type of lesion

From a total of 362 articles, we randomly selected 50 articles (22 from Stroke, 13 from the Journal of Neurology, 15 from Cerebrovascular Diseases), consisting of 47 original articles and 3 case reports. The corresponding author was usually a neurologist (34/50, 68%). A radiologist was included in the authorship in 13 (26%) articles, of whom 8/13 (62%) were general radiologists, and 5/13 (28%) neuroradiologists (i.e. a neuroradiologist contributed to 10% of papers overall).

Thirty (60%) studies concerned acute and 7 (14%) old, lacunar lesions, and 13 (26%) studies concerned both. Thus, a total of 43 articles were relevant for definitions of acute, and 20 of old, lacunar lesions.

4.4.2. Imaging definitions

Terminology and definitions for lacunar lesions: Thirteen different terms were used for acute and 10 for old lacunar lesions (Table 4.2). 'Lacunar infarct' and 'lacunar stroke' were used for both acute and old lesions.

A definition for lacunar lesions was provided in 26/43 (60%) articles describing acute and 8/20 (40%) describing old lesions. Amongst these, 13 articles concerned both acute and old lesions, of which most (6/13, 46%) failed to provide a definition for either type of lesion, 4 /13(31%) provided a definition for only one lesion type, 1/13 (8%) used the same definition for both, and only 2/13 (15%) provided a separate definition for each.

Imaging descriptors for lacunar lesions: site, size and shape: Lacunar lesion site was defined in 18/43 (42%) studies of acute and 4/20 (20%) of old lesions with marked variation in descriptions (Table 4.3a); size was provided in 21/43 (49%) and 9/20 (45%), respectively, with a greater maximum size used for acute (25mm) vs old (20mm) lesions (Table 4.3b).

EPVS and their differentiation from lacunes: A description of EPVS was given in 7/50 (14%) articles (all on acute lesions only), with 7 different descriptions given. Of studies on old lacunar lesions, most (17/20, 85%) articles did not distinguish EPVS from old lacunar lesions.

4.4.3. Clinical definitions

Thirty eight (76%) articles specified terminology used for the clinical stroke syndrome, of which the majority included the term 'lacunar' (Table 4.4). A clinical stroke classification system was used in 8/50 (16%) papers (six using a risk factor-based system (Adams et al. 1993), one a risk factor-free system (Bamford 191), and one a combination of systems. A clinical stroke definition was provided in 25/50 (50%) articles, with most (19/25, 76%) referring to a 'classical lacunar syndrome' (either with or without reference to associated imaging findings; Table 4.4). From 20 articles concerning old lesions, correlation with possible previous, relevant stroke symptoms was attempted only 2 (10%) cases.

4.4.4. Other imaging-related data

Use of MRI and details of readers: Amongst 43 studies concerning acute lesions, 22 (51%) used MRI and 7 (16%) used CT. Diffusion imaging was performed in 33%. Most (31, 72%) did not provide any details on timing of imaging in relation to onset of stroke symptoms. For old lesions, MRI was used in 15/20 (75%) articles, CT in 4 (20%) and both modalities in 1 (5%). MR sequences used to diagnose lacunar lesions were described in 11 (31%) studies concerning acute, and 7 (44%) concerning old, lacunar lesions. Most papers did not provide a description of lesion attenuation on CT or intensity on MRI.

Discipline, number and blinding of readers: Amongst the 20/50 (40%) articles providing details on who interpreted brain imaging, most (13/20, 65%) indicated that imaging was interpreted by non-radiologists (including at least one neurologist in 12 papers and a neuropathologist in 1). Overall, 17/50 (34%) studies provided information on blinding of readers, 6/50 (12%) indicated level of reader experience, and 23/50 (46%) the number of readers. Of these, 13/23 (57%) had 2 or 3 readers and 10/23 (43%) a single reader only.

4.5. Discussion

In a sample of 50 articles from the lacunar stroke literature, in which the corresponding author was most often a neurologist, there was marked variation in terminology and descriptions of imaging definitions of lacunar lesions. Any type of imaging definition was provided in 26 (60%) studies of acute and 8 (40%) of old, lacunar lesions, with the terms 'lacunar infarct' and 'lacunar stroke' used for both acute and old, symptomatic and asymptomatic lesions. Definitions were heterogeneous and often incomplete. A minority of papers attempted to differentiate old, cavitated lacunes from EPVS and to seek relevant previous symptoms. Clinical terminology also varied widely. A clinical stroke definition was provided in only 50% of studies. Most papers used a risk factor-based clinical stroke classification system. For acute lesions only a third of those using MRI used DWI. Non-radiologists interpreted images in most cases. Most studies did not describe lesion attenuation/signal intensity or diagnostic sequences used.

Strengths of our study included assessment of multiple aspects of definitions and terminology for both acute and old lacunar lesions. We selected articles at random from

three journals with a stroke focus, which are likely to be reasonably representative of articles in the rest of the stroke literature. We collected data on clinical, as well as imaging-related data, thus enabling a wider overall impression of potential problems relating to lacunar stroke research.

There are limitations of our study. We randomly selected 50 articles from a total of 362 articles in a PubMed search of three stroke-related journals, therefore our data represent a small sample of the lacunar stroke literature. We had planned to sample a larger proportion but there seemed little point when the first 50 papers yielded so much variation in imaging/clinical definitions of lacunar lesions and related methodologies. We did not attempt to provide a 'gold standard' for imaging definitions of lacunar lesions as this was not our primary aim.

On imaging, lacunar lesions are commonly defined as 3- to 15mm lesions found in the territory of deep perforating arteries, a definition which is often applied to all types of lesion, whether acute or old, symptomatic or asymptomatic. We found marked variation in completeness of lacunar lesion definition and lesion descriptions, with both limited radiological involvement and limited correlation of old lacunar lesions with relevant prior symptoms. These, combined with a marked heterogeneity in the reporting of other lacunar stroke-related methodology, such as provision of information on timing of imaging and MRI sequences performed, may be contributing to ongoing controversies in lacunar stroke (Davis and Donnan 2004, Futrell 2004, Norrving 2004). Additional contributory factors include bias in clinical classification systems (Adams et al. 1993, Jackson and Sudlow 2005), used in most papers in this study, misclassification of

cortical as lacunar stroke (and vice versa) based on clinical symptoms alone (Potter et al. 2010a), misclassification of symptomatic lacunar infarcts as WML due to only a proportion of genuine, DWI-proven symptomatic lacunar infarcts undergoing cavitation (Potter et al. 2010b), suboptimal detection of acute lacunar infarcts (especially with concomitant WML and without DWI), misclassification of old, cavitated lacunes due to difficulties differentiating these from EPVS, and limited information on previous relevant neurological symptoms.

We found multiple terms in use for both acute and old lacunar lesions. Both the terms 'lacunar infarct' and 'lacunar stroke' were used for acute and old lesions. This interchangeable use of terminology and definitions for all types of lacunar lesions (whether or not related to symptoms, and for lesions of varying appearances) infers a similar aetiology for each lesion, even though underlying aetiology may be heterogeneous (Wardlaw 2008).

Ultimately, a full appreciation of cerebral lesions in lacunar stroke can only be reached at the neuropathological level. However, even neuropathological assessment may be difficult and mortality in lacunar stroke is low. A standardised approach to the imaging definitions of lacunar lesions – including careful lesion description, using appropriate MRI sequences, correlation with relevant symptoms, and avoidance of assumptions about underlying aetiology - is essential. Harmonisation in the approach to lacunar lesion reporting may help towards an improved understanding of lacunar stroke and cerebral SVD, with its subsequent implications for improvements in patient management.

4.6. Tables

Table 4.1 Imaging and clinical data collected from 50 articles on lacunar stroke

Acute and old lacunar lesions	Old lacunar lesions only
Imaging-related data	Differentiation from EPVS
	Correlation with previous
Terms used	symptoms
Provision of an imaging definition	
Lesion descriptors: site, size, attenuation/intensity	
Use of the same or separate definitions	
Modality	
Timing in relation to acute symptoms	
Description of MRI sequences performed/used for diagnosis	
Related clinical data	
Clinical stroke terminology	
Provision of a clinical definition	
Stroke classification system used (risk factor-based or risk factor-free)	

EPVS, enlarged perivascular spaces; MRI, magnetic resonance imaging

Table 4.2. Terms used for acute (n=43) and old (n=20) lacunar lesions on imaging

Acute lacunar lesions (n=43)	n (%)	Old lacunar lesions (n=20)	n (%)
'Infarct'/'lesion'		No reference to age	
Lacunar infarct/lesion	22 (51.2)	Lacunar infarct/lesion	8 (40)
Subcortical infarct/lesion	6 (14)	Lacunar stroke	1 (5)
Subcortical MCA territory infarct	1 (2.3)	Subcortical lesion	1 (5)
Deep subcortical infarct	1 (2.3)	Deep infarct	1 (5)
Small, deep lesion	2 (4.7)	Small infarct	1 (5)
Deep brain/focal infarct	2 (4.7)	Reference to age	
Hypodense lesion[a]	1 (2.3)	Old lacunar infarct	1 (5)
Striatocapsular infarct	1 (2.3)	Chronic subcortical infarct	1 (5)
Lesion	1 (2.3)	Reference to symptoms	
'Stroke'		Silent lacunar infarct	4 (20)
Subcortical stroke	1 (2.3)	Non-specific/no reference to lesion	
Deep ischaemic stroke	1 (2.3)	Lesion	1 (5)
Non-specific/no reference to lesion		No reference to lesion	1 (5)
Focal hyperintensity on DWI	1 (2.3)		
No reference to lesion	1 (2.3)		

[a] On both computed tomography and magnetic resonance imaging

MCA, middle cerebral artery; DWI, diffusion-weighted imaging

Table 4.3 Description of site (A) and size (B) for acute and old lacunar lesions on imaging

A. Acute lacunar lesions	n (%)
Site defined	18 (42)
General description	
Areas supplied by deep perforants	7 (38.9)
Subcortical MCA territory	1 (5.56)
Specific territories	
Supratentorial white matter	1 (5.56)
CR, BG, CS, IC or other deep white matter regions	1 (5.56)
BG and subcortical white matter	1 (5.56)
Deep white matter or brainstem	1 (5.56)
IC, thalamus, BG, CR, pons and CS	1 (5.56)
Lentiform nucleus	1 (5.56)
Thalamus, capsule, protuberance and mesencephalon	1 (5.56)
Subcortical, i.e. CR, IC and BG	1 (5.56)
CR, BG, thalamus and caudate nucleus	1 (5.56)
IC, CR, CS, CN, P, GP, thalamus, midbrain, pons and medulla	1 (5.56)

Old lacunar lesions (n=4)	n (%)
Site defined	4 (20)
Territory supplied by deep/superficial small perforating arteries	1 (25)
Deep in the brain	1 (25)
Frontal, parietooccipital, temporal, BG and infratentorial regions[a]	1 (25)
IC, thalamus, BG, CR, pons and CS	1 (25)

[a]As used for white matter hyperintensities

MCA, middle cerebral artery; CR, corona radiata; BG, basal ganglia; CS, centum semiovale; IC, internal capsule; CN, caudate nucleus; P, putamen; GP, globus pallidus

Table 4.3 continued

B.

	Acute lesions, n (%)	Old lesions, n (%)
Size defined	21 (49)	9 (45)
Minimum size stated[a]	4 (9)	6 (30)
Maximum size stated[b]	19 (44)	8 (40)

[a]Acute lesions, values 3-5mm; old lesions, range 10-20mm

[b]Acute lesions, values 2-, 3-, 5mm; old lesions, range 10-20mm

Table 4.4 Clinical terminology and descriptions used for lacunar stroke

A.	n (%)
Lacunar stroke/syndrome/infarction	28 (75.7%)
Lacunar, large vessel cervical or intracranial atherosclerosis	1 (2.7%)
Ischaemic stroke	2 (5.4%)
Subcortical MCA territory infarction/lacunar syndrome	1 (2.7%)
Subcortical stroke/lesion/infarction	3 (8.1%)
Acute focal symptoms e.g. hemiparesis or acute aphasia, diagnosed according to ICD-9	1 (2.7%)
Pure sensory stroke	1 (2.7%)
Cerebrovascular attack	1 (2.7%)

B.	n (%)
Lacunar syndrome (with or without description of each of the 5 classical syndromes)	14 (56)
Lacunar syndrome with reference to imaging findings	5 (20)
Symptoms specific to condition under investigation	1 (4)
Non-specific	
Acute focal deficit confirmed by an associated lesion on CT or MRI	1 (4)
Focal neurological symptoms	1 (4)
Minor focal cerebrovascular events	1 (4)
Ischaemic stroke	1 (4)
Syndrome associated with lacunar infarction in the deep white matter or brainstem	1 (4)

MCA, middle cerebral artery; ICD, International Classification of Diseases; CT, computerized tomography; MRI, magnetic resonance imaging

Chapter 5. Wide variation in definition, detection and description of lacunar lesions amongst researchers in cerebral small vessel disease

5.1. Introduction

Lacunar stroke accounts for about 25% of ischaemic stroke (Bamford et al. 1991). On brain imaging, lacunar lesions form part of a spectrum of radiological features of cerebral SVD. Lacunar and other SVD lesions may have overlapping appearances, e.g. recent, small, lacunar infarcts may be difficult to distinguish from WML without DWI or prior imaging; and old lacunar cavities may resemble EPVS. Some lacunar infarcts may never cavitate, and instead resemble a WML indefinitely (Potter et al. 2010b), making cavitation an unreliable marker for prior lacunar infarction.

A recent survey of 13 neuropathology laboratories showed wide variation in how lacunar infarcts and SVD features were defined (Pantoni et al. 2006). A literature review showed wide variation in reporting of lacunar-related lesions on imaging (Potter et al. 2010c). Variations in terminology have complicated research in other related areas such as vascular dementia (Chui et al. 2000, Erkinjuntti et al. 1997, Leys and Pasquier 1998, Pohjasvaara et al. 2000, Román et al. 1993). Radiological criteria for vascular dementia, especially those applying to small vessels, are also variable (van Straaten et al. 2003).

Variations in imaging definitions of lacunar lesions, difficulties in their detection, and variation in lesion classification, once identified, may be hampering lacunar stroke research.

5.2. Aims

We used an online survey (SurveyMonkey™; SurveyMonkey.com, Portland, Oregon, USA; R. Finley) to assess how researchers interested in cerebral SVD (1) use terminology and definitions for lacunar lesions and (2) detect and describe lacunar lesions.

5.3. Methods

We set up an online survey to send to researchers with an interest in cerebral SVD. We asked questions about participant discipline, whether they had previously published on lacunar stroke, and, where relevant, whether there had been involvement of a radiologist in reading of images in any previous publications.

To assess definitions of lacunar lesions, we asked participants to select a single answer from a list of several options for (1) size of lacunar lesions, (2) site of lacunar lesions and (3) definition of EPVS.

To assess detection and description of lacunar lesions, we used 10 case-based examples of brain CT and MRI. MRI sequences used in the case-based examples included axial T2, FLAIR and DWI (indicated on the images themselves). We provided a size marker on the image, or description of lesion size, in each case. We included a 'comments box' for all questions to allow queries, difficulties, further explanations and other relevant comments to be noted by participants. In the case-based examples, we assessed lesion detection and description, tested effects of lesion appearance (cavitation, size, location), presence of concomitant WML, and effect of providing prior imaging on lesion

detection. We deliberately chose images which allowed us to test one or several of these features, and included varying amounts of relevant prior information. We also assessed differentiation of lacunes from EPVS. For case-based examples of old lacunar lesions, we showed MRI T2 and FLAIR sequences (while withholding the DWI-positive imaging from the time of acute lacunar stroke presentation), provided a history of symptoms in the relevant hemisphere from the time of original presentation, and indicated that no haemorrhage was visible on GRE imaging. To assess degree of certainty in lesion detection, we asked participants to indicate if they thought the lesion was present: ‘yes, definitely’, ‘yes, probably’, ‘yes, possibly’, or ’no’.

We identified SVD researchers from a literature review of lacunar lesion definitions from three journals related to stroke (Stroke, Journal of Neurology, Cerebrovascular Diseases) and from prior knowledge amongst our stroke research group (e.g. previous collaboration, discussion at stroke research meetings). We tested the survey in our dedicated stroke research group prior to the final, modified version being sent 'live'. A web link to the survey was sent to 147 SVD researchers. We indicated in the covering email message that the survey would take approximately 10-15 minutes to complete, that partially completed surveys could not be saved, and that all responses would be anonymous (Appendix 6). We allowed three weeks for completion initially, and sent two further reminders, extending the deadline for completion of the survey by a further two weeks each time. We also encouraged sending of the survey link to other interested colleagues.

5.3.1. Analysis

We assessed the number of participants completing each question, their discipline, and previous publication on lacunar stroke (including involvement of a radiologist). For definitions of lacunar lesions and EPVS, we assessed the number of participants selecting each of the definitions provided. In the case-based examples, we assessed effects of lesion appearances (cavitation, site, size), concomitant WML and provision of prior imaging on lacunar lesion detection/description, and differentiation of lacunes from EPVS. We also downloaded an abbreviated summary of the results from the SurveyMonkey™ site (Appendix 7, including survey images).

5.4. Results

Fifty-six people responded to the survey, of whom 46/56 (82%) completed all 10 case-based questions, and 44/56 (79%) completed the entire survey (case-based and non-case-based questions). The majority of participants were neurologists (25/44, 57%). Other disciplines were stroke physicians (12/44, 27%), neuroradiologists (6/44, 14%) and a care of the elderly physician (1/44, 2%). Most respondents (37/44, 84.1%) had published articles on SVD, most with involvement of a radiologist (27/37, 73%).

5.4.1. Definitions of lacunar lesions and EPVS

For definition of site of lacunar lesions, most (43/44, 97.7%) respondents selected 'territory of deep perforating arteries – brainstem, BG and white matter' (Table 5.1). Definitions selected for size of acute and old lacunar lesions were more varied: for 'acute lacunar infarct'; 17/44 (38.6%) selected 3-20mm and 9/44 (20.5%) selected 3-

25mm (Table 5.1), and for 'old lacunar infarct', 27 (61.4%) selected 3-15mm (one participant selected 3-25mm). Numbers selecting each size category (3-15mm, 3-20mm, 3-25mm) were similar for both 'old lacunar infarct' and 'lacune'.

For EPVS definition, most (27/44, 61.4%) selected 'small, round or linear lesions along the course of penetrating arteries with intensity close to CSF' (Table 5.1). Definitions we provided which did not include specific size criteria were selected more often than those which did (32/44, 72.7%, vs 11/44, 25%, respectively; Table 5.1).

5.4.2. Effect of lacunar lesion appearance (cavitation and size), concomitant WML and prior imaging on old lacunar lesion detection and description

There was a strong tendency to identify CSF-containing cavities as lacunar infarcts. Thus, cavitated lesions were identified as lacunar stroke lesions with certainty by 29/46 (63%) participants (Figure 8A). In the presence of concomitant WML, cavitated lesions were much more likely to be identified as lacunar stroke lesions than non-cavitated lesions (29/46, 63% vs 4/51, 7.8%, respectively, Figure 8A, B; χ^2 p=<0.001), even if baseline FLAIR images were provided for comparison (Figure 8C). Indeed, when shown a CT scan with a cavity of CSF density in the thalamus (without information on whether the original presenting lesion was a haemorrhage or infarct), most respondents selected 'lacunar infarct' (25/56, 44.6%, Figure 9). Non-cavitated lesions were only identified as lacunar stroke lesions when large and in the absence of other WML (33/50, 66%, Figure 8D).

5.4.3. Differentiation between lacunes and EPVS

Prominent EPVS were more likely to be mistaken for lacunar infarcts than correctly identified as EPVS. Most participants counted EPVS as lacunes (e.g. 21/47, 44.7%, selecting '>5 lacunes' when shown the example in Figure 10).

5.4.4. Effect of lacunar lesion site

Lesion description varied with lesion site, being greatest for a lacunar lesion located in the brainstem. From a list of multiple terms provided, 20/56 (35.7%) opted to provide an alternative description for the brainstem lesion, many of which implied an underlying mechanism (Figure 11).

5.5. Discussion

In an online survey of SVD researchers, we found marked variation in definitions, detection and description of lacunar lesions, with even more variation in terminology when describing posterior fossa lesions. Most agreed on definitions for lacunar lesion site and EPVS but there was less agreement for lacunar lesion size. There was wide variation in lesion recognition and classification. Cavitated lesions of any size were detected with the highest degree of confidence, but were described using multiple terms, including 'lacunar infarct' and 'lacunar stroke' (even without information about possible previous haemorrhage or relevant symptoms). Detection of non-cavitated lacunar infarcts in the presence of WML, and differentiation of lacunes from EPVS, was poor.

The main strengths of our study were the use of a structured survey designed to assess multiple aspects of lacunar lesion description and detection. We tested the survey amongst local stroke researchers to improve the design and relevance of the survey prior to its distribution. The images were carefully chosen to allow us to test specific features that might influence lacunar lesion detection and description. We included images demonstrating various SVD features which we expect to be representative of the type of imaging being assessed by other lacunar stroke research groups. By specifically identifying researchers with an interest in cerebral SVD, we gathered opinions which are likely to be most relevant to lacunar stroke research.

Our study has limitations. Only a third of those invited to participate took part. The reasons for non-participation and any differences between participants/non-participants are unknown as the responses were anonymous. Not all participants completed the entire survey. Forty-four people completed the entire survey, so our data represents only a fraction of opinions; however, most respondents were interested in SVD, therefore we feel the responses were sufficient in both detail and quality to demonstrate the substantial lack of harmony for definitions and detection of lacunar lesions, even amongst interested experts. Most respondents were neurologists, with only a few neuroradiologists and one stroke physician; however neurologists have contributed the highest proportion of the lacunar stroke literature. In most cases, we allowed only a single answer, but participants were able to add further comments using a ‘comments box’.

We found marked variation in terminology for lacunar lesions, particularly for those in the brainstem, and a worrying tendency to infer causation rather than simply to describe the imaging appearance. Similar heterogeneity was found in a study of neuropathology laboratories (Pantoni et al. 2006). There was interchangeable use of the terms 'lacune', 'lacunar infarct' and 'lacunar stroke' for all lacunar lesions, whether recent or old, symptomatic or asymptomatic. This implies a similar etiology for each lesion, which may not be true (Wardlaw 2008). Identification of old lacunar lesions was best for cavitated lesions, but since only a fifth of symptomatic lacunar infarcts cavitate, cavitation is an unreliable marker for prior lacunar infarction (Potter et al. 2010b). Misclassification of old lacunar infarcts as WML, combined with variation in terminology, may be contributing to current sources of controversy in epidemiological, etiology and risk factor studies of lacunar stroke (Davis and Donnan 2004, Futrell 2004, Jackson and Sudlow 2005, Lammie and Wardlaw 1999, Lee et al. 2005a, Leys et al. 1999, Norrving 2004, Read et al. 1998, Wardlaw et al. 2009).

In conclusion, detection and description of lacunar lesions on imaging varies widely, with under-recognition particularly of old, non-cavitated lacunar lesions. A consensus in lacunar lesion definition - with more consistent and accurate use of the several terms currently in use for lacunar lesions, accurate lesion description and avoidance of assumptions about underlying cause – is urgently needed.

5.6. Tables

Table 5.1 Definitions of lacunar lesions and enlarged perivascular spaces (single answer allowed; n=44 except where indicated)

"What do you consider the best definition of size for the following lacunar lesions?"	3-15mm	3-20mm	3-25mm	Unsure
Acute lacunar infarct, n (%)	13 (29.5)	17 (38.6)	9 (20.5)	4 (9.1)
Old lacunar infarct, n (%)	27 (61.4)	12 (27.3)	1 (2.3)	3 (6.8)
Lacune, n (%)[a]	24 (55.8)	9 (20.9)	1 (2.3)	7 (16.3)

[a] n=43

"What do you consider the best definition regarding site of lacunar lesions?"	n (%)
Territory of deep perforating arteries - brainstem, basal ganglia (caudate nucleus, lentiform nucleus, internal capsule, thalamus) and white matter (corona radiata, centrum semiovale)	43 (97.7)
Subcortical MCA territory	0 (0)
Clinically relevant areas	0 (0)
Deep white matter of brain and/or brainstem	1 (2.3)
Deep in the brain	0 (0)

MCA, middle cerebral artery

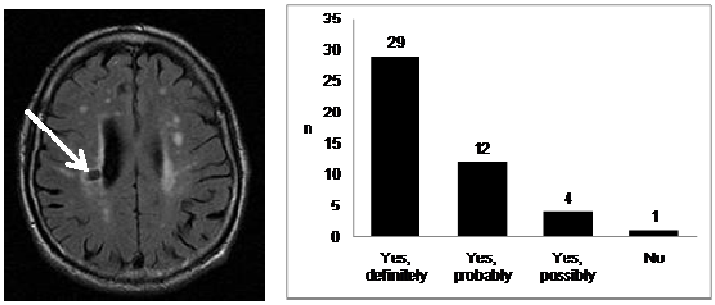
"What do you consider the best definition of enlarged perivascular (Virchow-Robin) spaces?"	n (%)
≤2mm, round or linear lesions along the course of penetrating arteries with intensity close to CSF	7 (15.9)
≤2mm, round or linear lesions at point of entry of MCA lenticulostriate arteries into basal ganglia, with intensity close to CSF	4 (9.1)
Small, round or linear lesions along the course of penetrating arteries, with intensity close to CSF	27 (61.4)
Small, round or linear, lesions at point of entry of MCA lenticulostriate arteries into basal ganglia, with intensity close to CSF	5 (11.4)
Uncertain	1 (2.3)

CSF, cerebrospinal fluid; MCA, middle cerebral artery

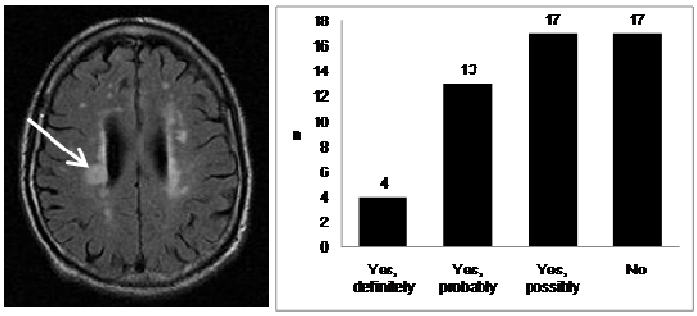
5.7. Figures

Figure 8 Effect of cavitation and white matter lesions (WML) on detection of old lacunar lesions.

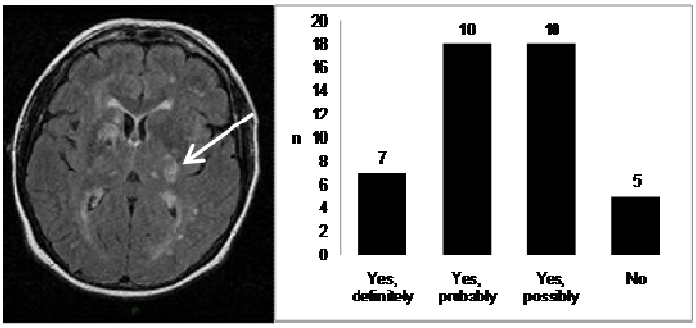
A. Cavitated lesion with WML ("Is there a lesion in the right hemisphere consistent with a lacunar infarct 18 months previously?; n=46)



B. Non-cavitated lesion with WML ("Is there a lesion in the right hemisphere consistent with a lacunar infarct 2 years previously?"; n=51)



C. Non-cavitated lesion with WML, but provision of baseline fluid-attenuated inversion recovery (FLAIR) imaging in survey ("Is there a lesion in the left cerebral hemisphere consistent with a lacunar infarct?; n=48)



D. Non-cavitated but large lesion, with no WML ("Is there a lesion in the right hemisphere consistent with a lacunar infarct 18 months previously?; n=50)

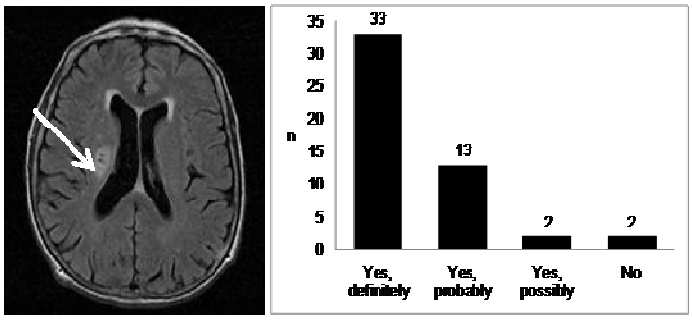
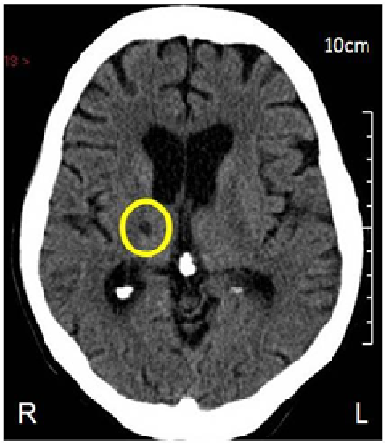


Figure 9 Effect of lesion appearance on lacunar lesion description

"Please indicate which term you consider most appropriate for the lesion circled in the right thalamus" (n=56)



	n (%)
Lacunar infarct	25 (44.6)
Lacunar stroke	3 (5.4)
Subcortical infarct	3 (5.4)
Subcortical stroke	0 (0)
Small, deep infarct	4 (7.1)
Small, deep stroke	3 (5.4)
Lacune	14 (25)
Black hole	3 (5.4)
White matter lesion	1 (1.8)
Other	0 (0)

Figure 10 Differentiation of lacunes from enlarged perivascular spaces (data shown for 47 respondents)

"How many lacunes are visible?" (T2 images shown in online survey)

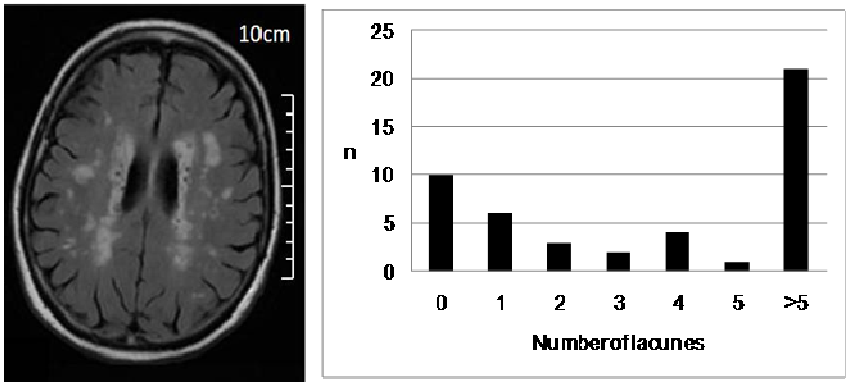
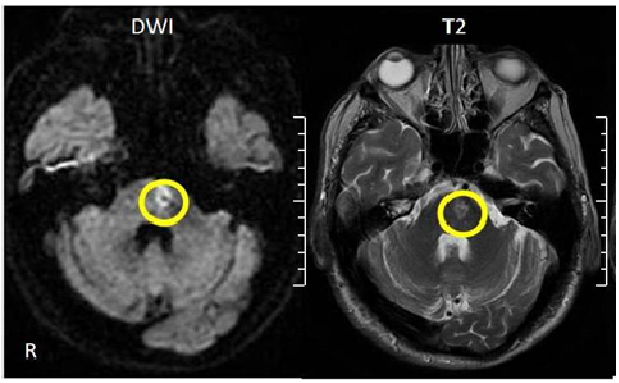


Figure 11 Effect of site of lacunar lesions on descriptions used

"Which term you consider most appropriate for this acute lesion in a patient with a 17-hour history of left pontine lacunar stroke symptoms?" (n=56; fluid attenuated inversion recovery (FLAIR) sequence not shown)



	n (%)
Lacunar infarct	23 (41.1)
Lacunar stroke	1 (1.8)
Subcortical infarct	1 (1.8)
Subcortical stroke	1 (1.8)
Small, deep infarct	9 (16.1)
Small, deep stroke	0
Lacune	0
Black hole	1 (1.8)
White matter lesion	0 (0)
Other*	20 (35.7)

*Other
Pontine infarct (n=6)
Probable infarct - lacune
Branch artery infarct
Branch artery disease
Pontine paramedian infarct (n=3)
Pontine branch infarct
Hyperintense vascular lesion in brainstem
Ischaemic lacunar stroke
Pontine perforator stroke
Left pontine ischaemic lesion
Brain or pontine infarction in paramedian territory, not lacunar
Lacunar stroke due to proximal perforator occlusion, suggesting large artery disease/embolism as the cause
Probably progressive subacute pontine infarct, given only rim of high DWI signal

Section two Neuroimaging of associated features of cerebral small vessel disease

Chapter 6. Lack of a relationship between carotid artery stenosis and ipsilateral white matter lesions suggests emboli do not cause white matter lesions

6.1. Introduction

WML, often termed 'leukoaraiosis' (Hachinski et al. 1987), are commonly seen on brain MRI, and are generally considered a marker of tissue damage from cerebral SVD. The precise cause of WML is unknown (Pantoni and Garcia 1997), but they are associated with increasing age, hypertension, diabetes, other vascular risk factors (Jeerakathil et al. 2004a), and markers of carotid atheroma such as intima media thickening and carotid plaques (Bots et al. 1993, Romero et al. 2009). Two studies have shown an apparent association between increasing degrees of carotid stenosis and WML (Romero et al. 2009, Saba et al. 2009), which has led to the suggestion that WML (and, by association, lacunar ischaemic stroke) may be caused by atherothromboemboli.

Amongst all studies that have assessed the relationship between carotid artery stenosis and WML, most have examined whole brain rather than hemispheric WML, using several methods of carotid stenosis measurement: tightest stenosis (Bogousslavsky et al. 1987, Lindgren et al. 1994, Manolio 1999, Romero et al. 2009); right carotid artery stenosis only (Bots et al. 1993); or stenosis graded basis according to presence of unilateral and/or bilateral carotid disease (Adachi et al. 1997, Fazekas et al. 1988,

Schmidt et al. 1992). Three studies have considered each hemisphere/carotid artery as separate units, with each patient contributing two pairs of scores, but two did not control for WML burden in the opposite hemisphere (Altaf et al. 2008, Saba et al. 2009), and the third, although adjusting for interdependence of right and left hemispheres, used CT to assess WML, which is less sensitive than MRI (Streifler et al. 1995). A single study of 20 patients assessed the relationship between carotid stenosis asymmetry and WML asymmetry (Herholz et al. 1990). Amongst all 12 previous studies, two (Romero et al. 2009, Saba et al. 2009) (n= 2118 patients) found an association between carotid stenosis and WML, and 10 (Adachi et al. 1997, Altaf et al. 2008, Bogousslavsky et al. 1987, Bots et al. 1993, Fazekas et al. 1988, Herholz et al. 1990, Lindgren et al. 1994, Manolio et al. 1999, Schmidt et al. 1992, Streifler et al. 1995) (n=5725) did not (Table 6.1). In addition to methodological differences (including methods of WML and stenosis measurement), these conflicting results may be attributed to whether or not studies accounted for associations with multiple overlapping risk factors, including age, as carotid stenosis and WML may both be associated with some other third variable, rather than directly with each other.

6.2. Aims

We hypothesized that if atherothromboemboli cause WML, then more WML would be expected to occur in the cerebral hemisphere distal to increasing degrees of carotid stenosis. In this study, we aimed to assess, in two large, separate, prospective cohorts of ischaemic stroke patients, the associations 1) between asymmetric carotid stenosis and

asymmetric WML and 2) between degree of carotid stenosis and ipsilateral hemispheric WML, while controlling for WML burden in the opposite hemisphere.

6.3. Methods

6.3.1. Patient recruitment

We recruited patients from the ESS and the MSS as described above. Briefly, the ESS consisted of prospectively recruited consecutive patients with stroke, admitted or seen as outpatients at a large academic teaching hospital, between 2002 and 2005; the MSS consisted of prospectively recruited consecutive patients, seen at the same hospital, with acute lacunar stroke, and control patients with mild cortical stroke, between 2005 and 2007. In this study, we included only patients with acute ischaemic stroke, where symptoms persisted >24 hours.

6.3.2. Clinical assessment, assessment of risk factors and investigations

Patients in both studies were assessed by an experienced stroke physician, who recorded baseline demographics, NIHSS score, and vascular risk factors. Hypertension and diabetes mellitus were defined as previous diagnosis of, or on current treatment for, hypertension or diabetes, respectively. In both studies, patients were assigned an OCSP classification (Bamford et al. 1991), which was modified following radiological assessment. Patients underwent routine stroke investigations, including brain CT or MRI, and carotid Doppler ultrasound. All patients from the MSS, and some from the ESS, had brain MRI instead of, or in addition to, CT. All patients included in the current study had MRI. Written informed consent was obtained from all patients (or guardians

of patients) in both studies. Both studies were approved by the Local Research Ethics Committee.

6.3.3. Brain and carotid imaging

Patients had carotid Doppler ultrasound of both carotid arteries using a 7.5 MHz linear transducer. Ultrasound was performed blinded to other imaging results, but not to clinical presentation. Carotid artery stenosis was defined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (NASCET Steering Committee 1991). The carotid artery contralateral to the side of symptoms was defined as symptomatic, and the artery ipsilateral to side of symptoms as asymptomatic.

6.3.4. Brain imaging and imaging classification

Brain MRI at 1.5T included axial diffusion- and T2WI, and axial FLAIR and other sequences as described above. Recent infarcts were defined as hyperintense on DWI, hypointense on the apparent diffusion coefficient map and either normal or hyperintense to brain on FLAIR/ T2WI, but less hyperintense than cerebrospinal fluid on T2WI. Brain MRI in each study was assessed by a neuroradiologist, who was aware of the side of acute stroke symptoms but blinded to other clinical and imaging data, including the presence of carotid disease. The studies were read at non-overlapping time points. The reader of the second study was unaware of the hypothesis being tested and was blinded to results of the first study. Each neuroradiologist (JMW, GMP) rated hemispheric WML on FLAIR and/or T2WI using the Fazekas scale (Fazekas et al. 1987), scoring 0-3 for deep and periventricular WML (where 0=none and 3=severe). To assess total

hemispheric WML, we combined scores in the hemispheric deep and periventricular regions. The less experienced neuroradiologist was trained in WML rating using a validated test set of 20 MRI scans demonstrating a full range of WML.

6.3.5. Analysis

We assessed the association between carotid stenosis (≥50% NASCET) asymmetry and WML asymmetry. We then assessed the association between degree of carotid stenosis (measured as a continuous variable) and WML score in the ipsilateral hemisphere, firstly without, then with, adjustment for potential confounders (age, diabetes and hypertension); we controlled for the opposite hemisphere by analysing left versus right , and symptomatic versus asymptomatic, sides for each patient. In the multivariate model, we dichotomised scores for overall (periventricular plus deep) WML (0, 0.5, 1.0 versus 1.5, 2.0, 2.5, 3.0, after halving periventricular and deep WML scores) and for periventricular and deep WML (0-1 vs 2-3). All statistical analyses were carried out using Minitab Statistical Software Version 15 (Minitab, Inc., State College, PA, USA).

6.4. Results

In the ESS, 253 acute stroke patients had brain MRI and carotid Doppler ultrasound, of whom 250 had imaging adequate for WML assessment. An additional three patients with primary intracranial haemorrhage were excluded, leaving 247 patients (mean age 69 ± 13 years). In the MSS, 253 patients with acute ischaemic stroke had brain MRI and carotid ultrasound (mean age 68 ± 11 years). Vascular risk factors and stroke severity were similar in both studies, with a low overall stroke severity score in both (Table 6.2).

A final OCSP classification (clinical plus imaging) of lacunar ischaemic stroke was present in 80 (32%) of patients in the ESS, vs 129 (51%) in the MSS. Median periventricular and deep WML scores were 1 (interquartile range 1-2) in both studies. Carotid stenosis on at least one side of ≥50% NASCET was present in 36 (15%) and ≥70% in 27 (11%) patients in the ESS, and 29 (11%) and 15 (6%) patients in the MSS (respectively).

Carotid stenosis was asymmetric in 28 (11%) and 26 (10%) patients in the ESS and MSS respectively (Table 6.3); of these, across both studies, only four had asymmetric WML (WML score higher distal to stenosed side in three and distal to the non-stenosed side in one). WML were asymmetric between hemispheres in 22 (9%) and 11 (4%) patients in the ESS and MSS, respectively; of these, across both studies, only four had asymmetric carotid stenosis (stenosis more severe proximal to the side with higher WML score in three, and to the side with lower WML score in one). Combining patients from both studies, there was no association between carotid stenosis asymmetry and WML asymmetry (OR 1.15, 95% CI 0.39 to 3.41).

Amongst 1000 hemispheres (over stenosis ranging from 0% to 100%), there was no association in either study between WML and ipsilateral carotid stenosis, whether symptomatic or not (Figure 12). This finding of a lack of an association was unchanged in multivariate analysis adjusted for potential confounders (Table 6.4). Increasing age was associated with periventricular, deep and overall WML in both studies, whether considering carotid stenosis as left and right ($p<0.001$ for periventricular and deep WML

and for overall WMH; Table 6.4), or as symptomatic and asymptomatic ($p<0.001$ for periventricular and deep WML and for overall WMH; Table 6.4).

6.5. Discussion

In this study of two large, separate cohorts of acute ischaemic stroke patients, there was no association between carotid stenosis asymmetry and WML asymmetry (OR 1.15, 95% CI 0.39 to 3.41). No association was found between increasing degrees of carotid artery stenosis and ipsilateral hemispheric WML, with or without adjustment for vascular risk factors. WML were strongly associated with increasing age in both studies ($p<0.001$).

The main strengths of this study were the inclusion of two separate, prospectively collected cohorts of stroke patients with similar baseline patient characteristics, totalling 500 patients, where brain appearances were assessed on MRI. Data collection methods were similar and comprehensive in each study and the same methods of brain and carotid artery imaging were used in all patients. Brain MRI was assessed by two independent neuroradiologists and both studies included patients with a full range of carotid stenosis and WML. We assessed the association between asymmetric carotid stenosis and asymmetric WML on a per patient basis and found no association. We performed detailed analysis of the relationship between hemispheric WML and ipsilateral carotid artery stenosis, while controlling for the opposite cerebral hemisphere WML load by considering each of the two artery-hemisphere units per patient as both right versus left, and symptomatic versus asymptomatic.

There were limitations to our study. The assessment of WML by a different neuroradiologist in each study might have led to inconsistencies, and could be considered a weakness; however, both neuroradiologists performed image reading to an internal standard using a validated test set. We made no adjustment for cardiac or aortic arch sources of emboli, but as these would not have any predilection for a particular hemisphere, this is unlikely to have any significant influence on our assessment of hemispheric WML distal to ipsilateral carotid stenosis. The inclusion of some patients with either high grade stenosis or carotid artery occlusion may have acted as a confounding factor due to the possibility of hypoperfusion-related WML (Fazekas et al. 1988), but the number of these was low in both studies. As relatively few patients had asymmetric stenosis (11% in the ESS, 10% in the MSS), we cannot fully exclude a direct association between WML and carotid stenosis; however, these frequencies of asymmetry for carotid stenosis are typical of hospital-admitted stroke patients and WML are generally symmetrical, so if an association between carotid stenosis and WML does exist, it is likely to be weak, indirect and occur via a co-association with a shared third factor. We considered combining the two datasets and analyzing them as one study, but we felt that it would be more correct to keep them separate as they were performed as separate studies and there were some differences in methodology. However, as both studies have independently arrived at the same conclusion, we do not feel that combining the data would have made a material difference.

Carotid artery stenosis is associated with cortical ischaemic stroke and transient ischaemic attack. Several studies suggest that carotid stenosis is infrequent in lacunar

stroke and may be coincidental (Mead et al. 2002), despite which, emboli are still regarded as a cause of lacunar stroke and WML. Amongst 12 previous studies (n=7843) assessing stenosis versus WML, two (n=2118) found an association between increasing stenosis and increasing global WML and 10 (n=5725) did not show any such association (Table 6.1). The populations in the studies are rather variable, only some adjusting for some risk factors or age, so it is possible that any association between stenosis and WML is actually due to co-association with a third factor which was not adjusted for. Three previous studies assessed the specific relationship between increasing degrees of carotid artery stenosis and ipsilateral hemispheric WML (n=1395) (Altaf et al. 2008, Saba et al. 2009, Streifler et al. 1995), but two relied on CT, which is less sensitive to WML (Saba et al. 2009, Streifler et al. 1995) (the rest used MRI), and the other was rather small (Altaf et al. 2008). Our results are in agreement with Herholz et al (Herholz et al. 1990), who assessed asymmetric WML versus asymmetric carotid stenosis, but in only 20 patients. Our multivariate results are in agreement with Altaf et al (Altaf et al. 2008), although they did not consider carotid artery/hemisphere units in relation to symptoms as we have done. Adding our 500 patients to these data means that there are now 11 studies, totaling 6225 patients, which have not shown any association between WML and carotid stenosis, including four which examined individual artery/hemisphere units; of these, ours is the only study to account for the opposite artery/hemisphere unit by considering left versus right, and symptomatic versus asymptomatic, sides.

In conclusion, in this study of two large cohorts of patients with ischaemic stroke, we found no link between degree of carotid stenosis and ipsilateral hemispheric WML,

whether the carotid stenosis was symptomatic or not. The totality of existing data would suggest that there is now substantial evidence that emboli have little role in the formation of WML (or by association, with most lacunar ischaemic stroke) and that any suggestion of an association in previous studies between embolic sources (e.g. atrial fibrillation or carotid disease) and WML may simply have been due to a third mediating factor, such as age or hypertension. Future studies should therefore focus on determining what causes the intrinsic small vessel pathological changes that appear to underlie most WML. Until the precise mechanisms underlying WML are elucidated, current therapies directed towards WML will likely remain focused on control of vascular risk factors.

6.6. Tables

Table 6.1 Previous studies investigating association between carotid artery stenosis measured by Doppler ultrasound* and white matter lesions (WML) (table continues on following page)

Study	n	Subjects	Type of imaging	WML rating method	WML location assessed	Findings	Association
Unilateral/highest % carotid stenosis (either side) vs global WML							
Romero et al. 2009	1971	Framingham Offspring Cohort (prospective epidemiologic study of young adults)	MRI	Volumetric, semiautomated	Global; location not stated	WML volume related to stenosis ≥50% after adjustment for vascular risk factors (OR 2.35, 95% CI 1.08-5.13)	Positive
Manolio et al. 1999	3502	Cardiovascular Health Study (cross-sectional study of men and women ≥65 years)	MRI	Visual rating scale	Periventricular, subcortical	WML associated with increasing severity of stenosis† (p=0.19)	Negative
Lindgren et al. 1994	77	Randomly selected patients ≥35 years with no history of focal brain lesions	MRI	Visual rating scale	Periventricular, deep	No relationship between WML and stenosis ≥50% (p=not significant)	Negative
Bogousslavsky et al. 1987	31	Patients with leukoencephalopathy and ischaemic stroke vs age- and sex-matched controls	CT	Visual description	Periventricular, centrum semiovale	Patients with WML less often had ≥50% stenosis‡ or occlusion vs controls (p<0.05) OR not given	Negative

Table 6.1 continued

Study	n	Subjects	Type of imaging	WML rating method	WML location assessed	Findings	Association
Right % carotid stenosis vs global WML							
Bots et al. 1993	111	Randomly selected patients aged 65 to 85 years from Rotterdam Scan Study (prospective follow-up of people aged ≥55 years investigating incidence of chronic disabling diseases)	MRI	Visual rating scale	Periventricular, deep	No difference in prevalence of minimal, or moderate to severe, stenosis§ (right carotid artery) between groups with/without WML	Negative
Unilateral/highest and/or bilateral stenosis vs global WML							
Schmidt et al. 1992	234	133 consecutive stroke patients and 101 normal volunteers	MRI	Visual rating scale (Fazekas 1997)	Periventricular, deep	No relationship between WML and stenosis‖ in multivariate analysis adjusted for vascular risk factors	Negative
Adachi et al. 1997	323	Patients with cerebrovascular disease, neurological disease, diabetes, ischaemic heart disease or medical examination of the brain	MRI	Visual, quantitative	Periventricular	No relationship between severity of periventricular WML and stenosis#	Negative
Fazekas et al. 1988	52	Volunteers in prospective field study on incidence of cerebrovascular risk factors	MRI	Visual description	Deep & subcortical	Higher grade stenosis** not detected in subjects with or without WML	Negative

Table 6.1 continued

Study	n	Subjects	Type of imaging	WML rating method	WML location assessed	Findings	Association
Unilateral % carotid stenosis vs ipsilateral hemispheric WML, each patient contributing two hemisphere-artery units							
Altaf et al. 2008	178	Recent anterior circulation TIA, minor strokes, and amaurosis fugax, and minimum 30% stenosis	MRI	Volumetric, semiautomated	Periventricular, subcortical	WML volume not related to degree of ipsilateral stenosis (p=0.60)	Negative
Saba et al. 2009	147	Consecutively registered patients ≥65 years undergoing CT of brain and carotid arteries	CT	Visual rating scale (Fazekas 1997)	Hemisphere	Association between WML and carotid stenosis class, adjusted for age and vascular risk factors (OR 1.365, 95% CI 1.073-1.737, p=<0.05)	Positive
Streifler et al. 1995	1197	Patients enrolled in NASCET with recent ischaemic symptoms and no cardiac source of embolism	CT	Visual rating scale	Periventricular	WML not related to degree of ipsilateral stenosis*** (OR [severe vs mild stenosis] 1.08, 95% CI 0.73-1.62; p=0.952)	Negative
Carotid stenosis asymmetry vs hemispheric WML asymmetry							
Herholz et al. 1990	20	Patients evaluated because of suspected cerebrovascular disease	MRI	Visual rating scale	Hemisphere; location not stated	No correlation between hemispheric WML asymmetry and stenosis asymmetry (τ_b =0.35; p=0.074)	Negative

*Except Herholz, where stenosis measured by cathether angiography or Doppler ultrasound; stenosis graded 0, no stenosis; 1, <70% stenosis; 2, ≥70%; 3, occlusion

Table 6.1 continued

†Graded as 0%; 1-24%; 25-49%; 50-74%; 75-99%; and 100% stenosis
‡Graded: normal or <50% stenosis; 50-74%; 75-99%; occluded
§Graded normal; minimal (1-15% stenosis); moderate (16-49%); severe (≥50%)
‖Graded 0, no atherosclerotic lesion (ASL); 1, discrete ALS one side (<20%); 2, 20-50% one side or discrete ASL both; 3, 50-70% one side or 20-50% both; 4, >0% one side , 50-70% both, or occlusion one side; 5, ≥70% or occlusion both sides
#Graded 1-5: 1, no lesions; 2, <30% stenosis; 3, 30-75%; 4, ≥75%; 5, occlusion; grouped as: 1, unilateral grade 2 or lower; 2, bilateral grade 2 or unilateral grade 3; 3, bilateral grade 3 or unilateral grade 4; 4, bilateral grade 4 or above or unilateral grade 5
**Graded 0-3: 0, no lesion; 1, unilateral <20% stenosis; 2, bilateral <20% or unilateral 20-50% stenosis; 3, bilateral 20-50% or unilateral ≥50-70% stenosis
***Graded mild, <30% stenosis; moderate, 30-69%; severe, 70-99%; occluded; τb = tau beta statistic
MRI, magnetic resonance imaging; CT, computed tomography; OR, odds ratio; CI, confidence interval; TIA, transient ischaemic attack; NASCET, North American Symptomatic Carotid Endarterectomy Trial

Table 6.2 Baseline clinical and imaging characteristics for Edinburgh Stroke Study (ESS) and Mild Stroke Study (MSS) acute ischaemic stroke cohorts

	ESS n=247	MSS n=253
Demographics*		
Age in years (± SD)	69 ± 13	68 ± 11
Male (%)	133 (54)	165 (65)
Previous stroke (%)	45 (18)	23 (9)
Diabetes	25 (10)	36 (14)
Hypertension (%)	131 (53)	154 (61)
Previous AF (%)	40 (16)	22 (9)
Lacunar stroke subtype	80 (32)	129 (51)
NIHSS, median (IQR)	1 (0-3)†	2 (2-3)
Imaging parameters		
PVL‡, median (IQR)	1 (1-2)	1 (1-2)
DWML‡, median (IQR)	1 (1-2)	1 (1-2)

*Shown as n (%) unless otherwise indicated
†n=230
‡PVL and DWML rated according to Fazekas scale
SD, standard deviation; AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; PVL, periventricular white matter lesions; DWML, deep white matter lesions

Table 6.3 Association between carotid stenosis asymmetry and white matter lesions (WML) asymmetry in the Edinburgh Stroke Study (ESS) and Mild Stroke Study (MSS)

ESS

	WML asymmetric	WML symmetric	Total
Stenosis asymmetric	2[a]	26	28
Stenosis symmetric	20	199	219
Total	22	225	247

[a] WML score higher distal to stenosed side in both

MSS

	WML asymmetric	WML symmetric	Total
Stenosis asymmetric	2[b]	24	26
Stenosis symmetric	9	218	227
Total	11	242	253

[b] WML score higher distal to stenosed side, n=1; WML score lower distal to stenosis, n=1

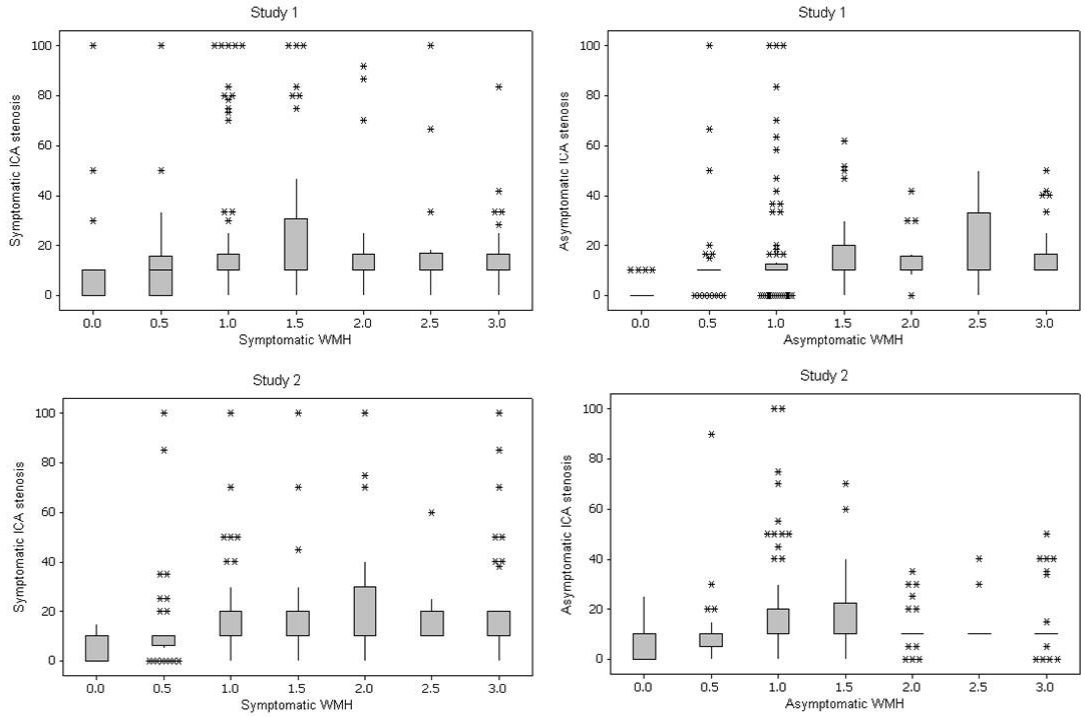
Table 6.4 Association between hemispheric white matter lesions (WML) and carotid artery stenosis adjusted for vascular risk factors for symptomatic/asymptomatic hemispheres, shown for the Edinburgh Stroke Study (ESS) and Mild Stroke Study (MSS)

	Symptomatic hemisphere WML				Asymptomatic hemisphere WML			
	ESS		MSS		ESS		MSS	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Increasing age	1.08 (1.05, 1.11)	0.000	1.11 (1.08, 1.14)	0.000	1.08 (1.06, 1.11)	0.000	1.11 (1.08, 1.15)	0.000
Diabetes	0.83 (0.33, 2.06)	0.685	0.91 (0.40, 2.04)	0.811	0.94 (0.37, 2.35)	0.888	0.78 (0.34, 1.76)	0.544
Hypertension	1.50 (0.85, 2.65)	0.162	1.01 (0.55, 1.86)	0.968	1.40 (0.79, 2.46)	0.250	0.96 (0.52, 1.79)	0.904
Carotid artery stenosis (%)	1.00 (0.99, 1.01)	0.865	1.01 (1.00, 1.03)	0.117	0.99 (0.98, 1.01)	0.418	0.99 (0.98, 1.01)	0.476

OR, odds ratio; CI, confidence interval

6.7. Figures

Figure 12 Relationship between hemispheric white matter lesion (WML) and ipsilateral carotid stenosis (% NASCET) in the ESS (Study 1) and the MSS (Study 2), showing symptomatic versus asymptomatic sides.



Chapter 7. Are enlarged perivascular spaces associated with white matter hyperintensities and lacunar stroke?

7.1. Introduction

Perivascular spaces (PVS), or Virchow-Robin spaces, surround the walls of arteries, arterioles, veins and venules as they course from the subarachnoid space through the brain parenchyma (Kwee and Kwee 2007). PVS are commonly seen on brain MRI but are frequently ignored or considered normal.

The pathophysiology of EPVS in unclear, but they may be part of the spectrum of age-related SVD, previous studies having shown an association with lacunar stroke (Adachi et al. 2000, Doubal et al. 2010), WMH (Doubal et al. 2010), CADASIL (Cumurciuc et al. 2006) and vascular dementia (Patankar et al. 2005). Similarly, the diagnostic and prognostic significance of EPVS are not fully known at present. EPVS appear in small numbers in all age groups, but their frequency increases with advancing age, in association with worse cognition in otherwise normal older subjects (MacLullich et al. 2004) and patients with diabetes (Ferguson et al. 2003), and in several disease states, including depression at older ages (Patankar et al. 2007), multiple sclerosis (Wuerfel et al. 2008), myotonic dystrophy (Di Costanza et al. 2001) and Parkinson's disease (Laitinen et al. 2000).

7.2. Aims

In this study, we tested the association of EPVS with WMH and lacunar stroke subtype in an independent cohort of ischaemic stroke patients.

7.3. Methods

7.3.1 Patient recruitment, clinical assessment, assessment of risk factors and investigations

We recruited patients from the ESS as described above. Briefly, patients were diagnosed and subtyped by a stroke physician using the OCSP classification into LACS, PACS, TACS and POCS (Bamford et al. 1991). Initial clinical classification was modified by radiological assessment. Patient demographics and risk factors were recorded, including age, history of diabetes, hypertension and previous clinical presentation with TIA or stroke (Jackson et al. 2008). In the current study we included only those patients with acute stroke who underwent MRI. The ESS was approved by the Local Research Ethics Committee and all patients (or their relatives) gave written informed consent.

7.3.2. Brain imaging and imaging classification

Patients underwent 1.5T MRI (GE Signa LX EchoSpeed scanner, Milwaukee, WI, USA) as described above. Images were reviewed by a neuroradiologist (GMP) who was blinded to all clinical details except for age and sex (present on MR images). Location and size of recent infarcts were recorded. Recent infarcts were defined as hyperintense on DWI/hypointense on the apparent diffusion coefficient map, and either normal or hyperintense to normal brain on FLAIR/T2 imaging (less hyperintense than cerebrospinal fluid on T2). Acute lacunar infarcts were defined as round or ovoid lesions measuring ≤20mm in maximal diameter in the white matter, BG or brainstem. EPVS (defined as ≤2mm round or linear CSF-isointense lesions along the course of

penetrating arteries, T2-hyperintense and T1/FLAIR-hypointense) were rated on T2 imaging (with all sequences available) in the BG and CS using a local rating scale from 0-4, where 0=none, 1=1-10, 2=11-20, 3=21-40 and 4=>40 EPVS (MacLullich et al. 2004). Total EPVS scores were calculated by combining CS EPVS (CS-EPVS) and BG EPVS (BG-EPVS) scores to give a score of 0-8. Periventricular and deep WMH were rated 0-3 using the Fazekas method (Fazekas et al. 1987). The neuroradiologist was familiarised with the WMH rating scale using a local validated test set of images. We recorded presence of old infarcts (using all sequences) and rated deep and superficial cerebral atrophy from 0-3 using a validated scale, where 0=none and 3=severe (Farrell et al. 2009).

7.3.3. Analysis

Total EPVS were normally distributed and were analysed using multiple linear regression. We assessed univariate associations of EPVS using the Pearson correlation for age, the Student's t-test for dichotomised variables (previous stroke, diabetes, old infarcts and presence of lacunar stroke subtype) and linear regression for WMH. We used multiple regression to assess effects of explanatory variables (age, previous stroke, hypertension, diabetes, periventricular WMH, deep WMH, old infarcts, atrophy and lacunar stroke subtype) in predicting number of total EPVS. We assessed univariate and multivariate associations of BG- and CS-EPVS. BG- and CS-EPVS were not normally distributed and were dichotomised as 0-1 vs 2-4 to permit binary logistic regression. We dichotomised scores for WMH (0-1 vs 2-3) and for atrophy (combining superficial and deep atrophy scores to give a score 0-6, then dichotomising as 0-3 vs 4-6). Patients with both PACS and TACS were considered as cortical stroke.

All analyses were performed using Minitab Statistical Software Version 15 (Minitab, Inc., State College, PA, USA).

7.4. Results

We recruited 298 patients with a mean age of 68 years (Table 7.1). Eighty-nine (29.9%) patients were diagnosed with LACS, 113 (37.9%) with PACS, 20 (6.7%) with TACS and 69 (23.2%) with POCS. Clinical diagnosis was uncertain in seven (2.3%). Mean total EPVS score was 4, and the median score for periventricular WMH and deep WMH was 1; a higher atrophy category was present in 61 (20.5%) patients (Table 7.1).

7.4.1. Associations of total EPVS

Total EPVS were associated with increasing age, hypertension, periventricular WMH and deep WMH (all p<0.001), atrophy (p=0.001) and old infarcts (p=0.04; Table 7.2). In multivariate analysis after adjustment for vascular risk factors and periventricular WMH, only age (p=0.01) and deep WMH (p=0.005) remained significantly and independently associated with total EPVS; previous stroke also showed a significant association (Table 7.2).

7.4.2. Associations of BG- EPVS

On univariate analysis, BG-EPVS were associated with age, periventricular WMH, deep WMH, CS-EPVS and atrophy (all p=<0.001, Table 7.3). On multivariable analysis, only age (p=0.001), CS-EPVS (p<0.001) and atrophy (p=0.03) remained

significant. There was also a significant association between BG-EPVS and lacunar stroke subtype (p=0.04; Table 7.3).

7.4.3. Associations of CS-EPVS

On univariate analysis, CS-EPVS were associated with age (p=0.002), periventricular WMH (p=0.01) and BG-EPVS (p=<0.001); only BG-EPVS showed a significant association with CS-EPVS in multivariate analysis (p=<0.001), correcting for all other explanatory variables in the table (Table 7.4).

7.5. Discussion

Amongst 298 patients with ischaemic stroke, total EPVS were associated with age, deep WMH and previous stroke on multivariate analysis after adjustment for vascular risk factors and periventricular WMH. In multivariate analysis, BG-EPVS were associated with lacunar stroke subtype, increasing age, CS-EPVS and atrophy.

There were strengths in our study. We used a cohort of prospectively recruited patients with acute ischaemic stroke who were carefully assigned an OCSP subtype by an experienced stroke physician using a combination of clinical and radiological assessment. All patients underwent standardised brain MRI. We used a large cohort of patients, enabling us to assess several possible explanatory variables. We assessed EPVS associations using both combined (BG- and CS-EPVS) as well by separate BG and CS locations, which enabled us to compare EPVS associations between these sites. EPVS were assessed using a rating scale previously shown to have high intrarater agreement (MacLullich et al. 2004) and which allowed us to record a full range of

EPVS, from none to >40. We performed multivariate analysis in order to correct for as many confounding factors as possible.

Limitations to our study include the use of a single image rater. However, 'recalibration' using a test set of images was performed during rating in order to try and minimise intra-rater variability.

At present, the diagnostic and prognostic significance of EPVS are not fully known. Our findings of an association between BG-EPVS and WMH are similar to findings by Doubal et al (2010), although our patient cohorts were slightly different. Our findings of an association with age and WMH are also in agreement with Rouhl et al (Rouhl et al. 2008), who found association between BG-EPVS and age, hypertension, asymptomatic lacunar infarcts, and WMH. However, these associations were investigated in patients with a first lacunar stroke, rather than in a cohort including all stroke subtypes.

The causes for EPVS are unclear. Blood-brain barrier dysfunction may play a role in the aetiology of lacunar stroke (Wardlaw et al. 2009) and in patients with multiple sclerosis, in which EPVS become more visible with development of active inflammation and subside again as inflammatory activity wanes (Wuerfel et al. 2008). EPVS are conduits for drainage of interstitial fluid from the brain (Abbott 2004, Warlow et al. 1992), so it is highly relevant if they alter in visibility with inflammation, given that SVD may have an inflammatory component. EPVS are also more frequent compared to healthy controls in CADASIL (Cumurciuc 2006) where there is altered vessel wall permeability and extravasation of plasma proteins into the PVS (Poirier et

al. 1983). It seems plausible that blood-brain barrier dysfunction may also play a role, as yet undefined, in the formation of EPVS.

Another hypothesis for the aetiology of EPVS includes ex-vacuo dilatation secondary to shrinkage of cerebral tissue after demyelination and axonal loss. In our study, we found an association between BG-EPVS and atrophy, but not between total or CS-EPVS and atrophy. However, no association between atrophy and EPVS was demonstrated in previous studies of patients with ischaemic stroke (Doubal et al. 2010) or multiple sclerosis (Wuerfel et al. 2008).

In conclusion, our study, showing an association between total EPVS and WMH, and between BG-EPVS and lacunar stroke, provides further evidence that EPVS may be a further imaging marker for cerebral SVD. Our findings should be confirmed in larger studies with similar patients. Given the growing evidence that EPVS are not as benign as once thought and may be part of the spectrum of SVD, EPVS should not be ignored, but included in the overall imaging assessment of cerebral SVD.

7.6. Tables

Table 7.1 Baseline characteristics of study subjects (n=298)

Characteristic	
Mean age in years (SD)	68.4 (13.3)
Previous TIA n (%)	51 (17.1)
Previous stroke n (%)	79 (26.5)
Hypertension n (%)	156 (52.3)
Diabetes n (%)	27 (9.1)
Lacunar stroke subtype n (%)	89 (29.9)
Deep WMH Fazekas score, median (IQR)	1 (1-2)
Periventricular WMH Fazekas score, median (IQR)	2 (1-2)
Atrophy n (%)	61 (20.5)
Old infarcts n (%)	89 (29.9)
Mean total EPVS score (SD)	4 (1.7)

SD, standard deviation; TIA, transient ischaemic attack; WMH, white matter hyperintensities; IQR, interquartile range; EPVS, enlarged perivascular spaces

Table 7.2 Univariate (A) and multivariate (B) associations with total (basal ganglia and centrum semiovale) enlarged perivascular spaces (EPVS)

A.

Variable	Statistic used and test score	p value
Age	Pearson coefficient 0.422	<0.001*
Previous stroke	t-test difference in EPVS score 0.033 (-0.393 to 0.460)	0.88
Hypertension	t-test difference in EPVS score -0.676 (-1.049 to -0.302)	<0.001*
Diabetes	t-test difference in EPVS score 0.356 (-0.294 to 1.005)	0.27
Periventricular WMH	Linear regression adj r squared 24.8%	<0.001*
Deep WMH	Linear regression adj r squared 22.6%	<0.001*
Atrophy	Linear regression adj r squared 3.4%	0.001*
Old infarcts	t-test difference in EPVS score 0.4 (0.02 to 0.779)	0.04*
Lacunar stroke subtype (compared with cortical stroke)	t-test difference in EPVS score 0.16	0.48

*Significant at p<0.05; WMH, white matter hyperintensities

B.

Variable	Beta coefficient	p value
Age	0.02	0.01*
Previous stroke	-0.27	0.006*
Hypertension	0.25	0.15
Diabetes	-0.31	0.31
Periventricular WMH	0.31	0.08
Deep WMH	0.44	0.005*
Old infarcts	-0.01	0.97
Atrophy	-0.003	0.42
Lacunar stroke subtype (compared with cortical stroke)	0.15	0.42

*Significant at p<0.05; WMH, white matter hyperintensities

Table 7.3 Univariate and multivariate associations for dichotomised basal ganglia enlarged perivascular spaces (EPVS)

Variable	Univariate p value	Univariate OR (95% CI)	Multivariate p value	Multivariate OR (95% CI)
Age	<0.001	1.08 (1.05-1.10)*	0.001	1.06 (1.02-1.09)*
Hypertension	0.015	1.78 (1.12-2.82)*	0.84	0.94 (0.50-1.76)
Diabetes	0.3	0.65 (0.29-1.46)	0.48	0.68 (0.24-1.98)
Deep WMH	<0.001	3.00 (2.19-4.11)*	0.22	1.43 (0.81-2.54)
Periventricular WMH	<0.001	3.48 (2.53-4.80)*	0.08	1.73 (0.95-3.15)
Old infarcts	0.05	1.59 (1.00-2.54)	0.4	0.76 (0.40-1.45)
CS-EPVS	<0.001	3.00 (2.21-4.07)*	<0.001	3.27 (2.20-4.85)*
Atrophy	<0.001	3.64 (1.95-6.81)*	0.03	2.72 (1.08-6.84)*
Lacunar stroke subtype (compared with cortical stroke)	0.26	1.36 (0.79-2.34)	0.04	2.08 (1.04-4.17)*

*Significant at p<0.05
OR, odds ratio per unit increase in the explanatory variable; CI, confidence interval; WMH, white matter hyperintensities; CS-EPVS, centrum semiovale enlarged perivascular spaces

Table 7.4 Univariate and multivariate associations for dichotomised centrum semiovale enlarged perivascular spaces (EPVS)

Variable	Univariate p value	Univariate OR (95% CI)	Multivariate p value	Multivariate OR (95% CI)
Age	0.002	1.03 (1.01-1.05)*	0.76	1.00 (0.98-1.03)
Hypertension	0.13	1.5 (0.89-2.52)	0.69	1.13 (0.63-2.01)
Diabetes	0.62	1.27 (0.49-3.28)	0.39	1.58 (0.56-4.46)
Deep WMH	0.07	1.29 (0.98-1.7)	0.29	0.75 (0.44-1.29)
Periventricular WMH	0.01	1.46 (1.1-1.93)*	0.72	1.11 (0.63-1.97)
Old infarcts	0.31	1.32 (0.77-2.24)	0.53	1.22 (0.66-2.23)
BG-EPVS	<0.001	2.56 (1.76-3.74)*	<0.001	2.96 (1.87-4.69)*
Atrophy	0.98	1.01 (0.53-1.91)	0.17	0.55 (0.24-1.30)
Lacunar stroke subtype (compared with cortical stroke)	0.47	0.8 (0.44-1.46)	0.25	0.69 (0.37-1.29)

*Significant at p<0.05
OR, odds ratio per unit increase in the explanatory variable; CI, confidence interval; WMH, white matter hyperintensities; BG-EPVS, basal ganglia enlarged perivascular spaces

Chapter 8. Quantification of enlarged perivascular spaces (EPVS): development and observer variability of an EPVS rating scale

8.1. Introduction

EPVS surround the walls of arteries, arterioles, veins and venules as they course from the subarachnoid space through the brain parenchyma (Kwee and Kwee 2007). EPVS are normally microscopic and are thought to be visualised on T2-weighted brain MRI only when enlarged. Previous studies have suggested that EPVS may act as drainage pathways in the brain (Abbott 2004, Esiri and Gay 1990, Warlow et al. 1992), and when enlarged, may represent interstitial fluid trapped in the subpial or interpial space of the brain (Ozturk and Aydingoz 2002).

At present, the diagnostic and prognostic significance of EPVS are not fully known. Although EPVS appear in small numbers in all age groups, their frequency increases with advancing age, in association with worse cognition in otherwise normal older subjects (MacLullich et al. 2004) and patients with diabetes (Ferguson et al. 2003), and in several disease states including CADASIL (Cumurcuic 2006), depression at older ages (Patankar et al. 2007), multiple sclerosis (Wuerful 2008), myotonic dystrophy (Di Costanza et al. 2001) and Parkinson's disease (Laitinen et al. 2000). EPVS are also part of the spectrum of age-related SVD, previous studies having shown an association with lacunar stroke (Adachi et al. 2000, Doubal et al. 2010), WML (Doubal et al. 2010) and vascular dementia (Patankar et al. 2005).

Since the recognition of WML on cross sectional imaging in the 1980s, multiple WML rating scales have been developed (Fazekas et al. 2002), but EPVS are not included in any of these. Several EPVS rating scales have been described (Adachi et al. 2000, Di Costanza et al. 2001, Groeschel et al. 2006, Heier et al. 1989, MacLullich et al. 2004, Patankar et al. 2005, Rouhl et al. 2008), but these appeared limited in either the anatomical location or range of EPVS that they describe, or in their method of assessing frequency and severity. Knowledge of the observer variability of EPVS rating scales is essential if the diagnostic and prognostic significance of EPVS are to be investigated effectively. Previous testing of a local EPVS rating scale (MacLullich et al. 2004) showed good intrarater agreement for BG-EPVS and moderate agreement for centrum CS-EPVS.

8.2. Aims

We aimed to develop an improved scale and test its observer agreement.

8.3. Methods

8.3.1. Review of previously published EPVS rating scales and selection of a scale for revision

We searched for and reviewed previously published EPVS rating scales (Adachi et al. 2000, Di Costanza et al. 2001, Groeschel et al. 2006, Heier et al. 1989, MacLullich et al. 2004, Patankar et al. 2005, Rouhl et al. 2008; Table 8.1). A neuroradiologist (GMP) applied each scale on two occasions to a test set of 20 standard T2-weighted MR scans,

from older subjects with and without stroke symptoms, that had been selected to represent a range of WML, noting the ease of use and time required to become familiar with each scale. The scale used by MacLullich et al (MacLullich et al. 2004) appeared most comprehensive and easy to use and was selected for further revisions in an attempt to create an easy to use, comprehensive EPVS rating scale.

8.3.2. Development and testing of a revised EPVS rating scale

Regions to be assessed: We retained BG and CS regions (included in all but one of the previously published scales; Table 8.1) and added the midbrain (MB) (included in one previous scale; Table 8.1) as these are three major sites for EPVS (Kwee and Kwee 2007). We removed the hippocampus because of its variable visualisation on axial images and because hippocampal EPVS may be confused with hippocampal fissural cysts, currently thought to be normal variants. As most people will demonstrate EPVS in the anterior perforated substance (Groeschel et al. 2006), EPVS in this region are unlikely to be a reliable indicator of EPVS frequency or severity; we therefore chose not to add this to the revised scale. We did not separate EPVS into sub-regions in the BG (as done by Patankar et al (Patankar et al. 2005), as this was found to be both difficult and time-consuming; or in the CS (as done by Rouhl et al; Rouhl et al. 2008). We tested effects on rating consistency of using pre-defined slices and regions, e.g. for BG-EPVS, using the slice showing the maximal BG area, and for CS-EPVS, regions defined by pre-defined gyri and sulci, but since none of these methods led to an improvement in consistency, they were not incorporated into the revised scale.

Method of rating: We retained the frequency and range of EPVS used by MacLullich et al (MacLullich et al. 2004) as follows: 0=no EPVS, 1=1-10 EPVS, 2=11-20 EPVS, 3=21-40 EPVS, 4=>40 EPVS (Figure 13; Appendix 8). These categories are similar to those used by Rouhl et al. previously (Rouhl et al. 2008) and best reflect the possible frequency and range of EPVS, unlike previous scales in which EPVS range and frequency are limited (Adachi et al. 2000, Heier et al. 1989, Patankar 2005) or in which every individual EPVS requires to be counted (Di Costanza et al. 2001). Unlike two previous studies (Di Costanza et al. 2001, Heier et al. 1989), we did not include size criteria due to difficulties in distinguishing between EPVS measuring <2mm and 2-3mm. We used frequency and range of EPVS in preference to dichotomisation by appearance (dilated vs non-dilated; Groeschel et al. 2006, since we considered this a more sensitive and accurate method of EPVS assessment. Although excluded in one previous scale (Rouhl et al. 2008), we chose to include EPVS surrounded by a FLAIR-hyperintense rim, since although the exact nature of these is unclear, they are likely to form part of the same spectrum of cerebral SVD.

EPVS rating scale user guide: Prior to testing of the revised rating scale, we constructed a 'user guide' with detailed definitions, descriptions and clear examples (http://www.sbirc.ed.ac.uk/documents/epvs-rating-scale-user-guide.pdf; Appendix 9). EPVS were defined as small, sharply delineated structures of CSF intensity measuring ≤2mm following the course of perforating vessels. We provided examples for each rating category and for each region, gave instructions on slice selection, and highlighted potential difficulties, such as differences in EPVS visibility and presence of WML.

Following observer testing in the present study, we added further instructions to avoid the residual sources of observer disagreement.

Assessment of observer variability of the revised EPVS rating scale: Two different neuroradiologists (ZM, JMW), blinded to the other's ratings, tested the modified EPVS rating scale by each rating 60 T2-weighted MR scans (with T1-weighted, FLAIR, and GRE imaging also available) on two separate occasions. Images were reviewed by each rater at least one week apart and in a random order (using a web-based random number service, RANDOM.ORG) on each occasion. MRI scans were selected from a local hospital-based stroke registry (the ESS, Jackson et al. 2008; www.dcn.ed.ac.uk/ess/) and a cohort of older community-dwelling well people (the Lothian Birth Cohort 1936 Study; Deary et al. 2007) and assessed digitally using the national Kodak Picture Archiving and Communication System. The 60 MRI scans included a full range of EPVS and demonstrated varying background brain appearances, including WML and lacunes.

8.3.3. Analysis

We quantified observer agreement using the unweighted kappa (κ) statistic for EPVS grades after dichotomizing the five potential categories into categories 0-2 versus 3-4. Analyses were performed using the Statistical Package for the Social Sciences Version 14 (SPSS Inc., Chicago, IL, USA). Confidence intervals for κ and median scores for BG- and CS-EPVS were calculated using Minitab Statistical Software Version 15 (Minitab, Inc., State College, PA, USA).

8.4. Results

8.4.1. Intra- and interrater agreement for the modified EPVS rating scale

Between the first and second ratings, there was a trend towards higher BG- and CS-EPVS ratings for rater 1 (median scores 2 for BG-EPVS and CS-EPVS vs 3 and 2.5, respectively, on repeat rating) and a trend towards lower rating by rater 2 (median scores for BG-EPVS and CS-EPVS of 3 and 2, respectively, vs 2.5 and 2 on repeat rating; Table 8.2).

Intrarater agreement was similar in all locations, being good for CS- and MB-EPVS (κ range, 0.60 to 0.72) and highest for BG-EPVS (κ 0.73, 0.86 for rater 1, 2, respectively; table 8.2). Interrater agreement was moderate for CS- and MB-EPVS on both ratings (κ range 0.41 to 0.58) and highest for BG-EPVS (κ 0.86, initial rating; Table 8.2).

8.4.2. Sources of discrepancy using the modified EPVS rating scale

On close review of sources of discrepancy, it was clear that most disagreements were due to very small but visible EPVS, extensive WML or presence of multiple lacunes (Table 8.3; Figure 14). Very small EPVS could be discriminated by their intensity lower than CSF and we decided that these should not be counted as true EPVS. WML, especially when extensive and confluent, accounted for disagreements in the CS as the WML obscured EPVS. Lacunes contributed to disagreements in the BG region (Table 8.3). Disagreement also occurred when there was asymmetry in background brain parenchyma (due to a previous unilateral total anterior circulation infarction), and where

EPVS were asymmetrical (Table 8.3). EPVS with a surrounding FLAIR-hyperintense rim did not contribute to intra- or interrater disagreement.

8.5. Discussion

We reviewed existing EPVS visual rating scales, identified omissions or ambiguities in each, and used this combined knowledge to design improvements to one existing scale that already most closely met requirements for a comprehensive easy-to-use scale. Two other radiologists then tested this revised scale on 60 MRI scans chosen to demonstrate a full range of EPVS frequencies, backed by a comprehensive user guide with further modifications to help avoid residual sources of observer variation.

Using this revised scale, two observers showed similar intrarater agreement for BG-, CS- and MB EPVS (MB-EPVS) ranging from good to very good kappa values. Interrater agreement was moderate for CS- and MB-EPVS on both ratings although very good for BG-EPVS on the initial rating. Disagreements were mainly due to the counting of very small but just visible EPVS, which were a recognised source of difficulty prior to rating. Other main causes for disagreement were the presence of numerous background WML particularly when confluent and lacunes (in the CS and BG regions, respectively).

Strengths of our study included the deliberate selection of a large sample of cases illustrating all grades of EPVS and a range of background appearances. We developed our existing EPVS rating scale after reviewing and testing existing scales; the current scale is very quick to apply and includes the three main anatomical regions where EPVS

are found. We wrote a user guide for the rating scale, including instructions on slice selection, potential difficulties in EPVS rating and imaging examples for each EPVS category (http://www.sbirc.ed.ac.uk/documents/epvs-rating-scale-user-guide.pdf). We used routine structural MRI for EPVS assessment rather than specialised sequences. Each observer performed ratings at least one week apart blind to prior ratings and in a random order on each occasion, minimising effects of recall. Observer variability was tested for dichotomized EPVS; however, the scale we have devised also records EPVS frequencies over a total of five levels, which allows the opportunity for testing EPVS associations more closely if required.

There were limitations to our study. We did not assess atrophy, which may have an influence on EPVS size, but this was not the purpose of this study and the scale we have devised does not rate EPVS size. The scale was tested by two experienced neuroradiologists, but brain imaging in many research studies is performed by non-radiologists (Potter et al. 2010c) and many raters will be less experienced in reviewing MRI scans and in rating EPVS. We hope the inclusion of a user guide, with detailed imaging examples for each rating category, will help improve observer variability. We included EPVS with a surrounding FLAIR-hyperintense rim, even though the exact nature of these is unclear, but these were not a source of intra- or interrater disagreement.

Further work on ways of improving observer agreement about EPVS is needed, including training observers in the rating of EPVS. The use, and further development, of the EPVS rating scale may help future studies to answer outstanding questions about the

diagnostic and prognostic value of EPVS and will enable study comparisons and meta-analyses. Although we have developed and tested a visual rating scale, automated EPVS measurement methods may be possible with improved image processing algorithms in future, as has already occurred for WML rating (Jeerakathil et al. 2004a).

In conclusion, assessment of EPVS can be standardised to at least a moderate to good level of interrater agreement with a modified rating scale that takes account of all prior rating scales and improvements that we implemented following testing. Further modifications should include additional ways to deal with very small EPVS and concomitant WML and lacunes to reduce their effect on EPVS assessment variability.

8.6. Tables

Table 8.1 Summary of existing enlarged perivascular spaces (EPVS) scales

Study	Subjects	MRI technique	Locations assessed	Description of rating method	Observer variability
Rouhl et al. 2008	165 patients with first ever lacunar stroke	1.5T axial T2WI and FLAIR	CS, BG	Low=<20 EPVS, moderate=20-50 EPVS, high=>50 EPVS	Interobserver Cohen's kappas: BG-VRs, 0.64; CSO-VRs, 0.57; L-VRs, 0.72
Groeschel et al. 2006	125 healthy subjects aged 0.5-30 years; 26 clinical subjects undergoing MRI	Healthy subjects: 1.5T high-resolution 3D structural images using T1W 3D FLASH; clinical subjects: 1.5T, axial T2 TSE/SPIR and FLAIR, sagittal T2, coronal T1 IR-TSE	Supratentorial white matter	Dilated = focal expansion, either irregular or ectatic); non-dilated = smooth and regular morphology	NA
Patankar et al. 2005	75 patients with Alzheimer's disease; 35 healthy volunteers	1.5T axial FLAIR, T1W IR, variable echo, FSE, high-resolution 3D T1W fast field-echo	CS, BG, mesencephalon, subinsular region	CS: 0=none, 1=<5 per side, 2->5 on one or both sides; basal ganglia: 0=only either side and <5 either side, 2=>5 SI on either side or any in lentiform nucleus, 2=any in caudate nucleus on either side; subinsular: 0=none, 1=<5 either side, 2=>5 on one or both sides	Intrarater BG, 0.89-1.00; CS, 0.78/0.82; subinsular, 0.89, 0.91; mesencephalon 0.84, 0.94; interobserver BG 0.91, 0.98; CS 0.84; subinsular 0.90; mesencephalon 0.82

Table 8.1 continued

Study	Subjects	MRI technique	Locations assessed	Description of rating method	Observer variability
MacLullich et al. 2004	97 healthy men	1.5T structural imaging with axial FSE T2	CS, BG, hippocampus	0=none, 1=<10, 2=11-20, 3=21-40, 4=>40	Intrarater Cohen's kappas: 0.88 for BG; 0.78 for CS
Di Costanza et al. 2001	41 adults with myotonic dystrophy	0.5T sagittal T1, axial PD and T2W SE	Lenticulostriate, high convexity	Number multiplied by size category, where size 1=<2mm, 2=2-3mm and 3=>3mm	NA
Adachi et al. 2000	171 consecutive patients admitted with acute cerebral infarcts	1.5T T2WI, T1WI and PD	BG	Grade 0, no lesions; grade 1, 1-5 lesions; grade 2, 6-10 lesions; grade 3, >10 lesions	NA
Heier et al. 1989	816 out-patients undergoing MRI	3 spin echo sequences (600-800/20; 2000/40-80; sagittal 800/20)	Lenticulostriate, high convexity	1 (mild)=<2mm, 2 (moderate)=2-3mm, 3 (marked)=>3mm	NA

MRI, magnetic resonance imaging; T2W, T2-weighted; FLAIR, fluid attenuated inversion recovery; CS, centrum semiovale; BG, basal ganglia; BG-VRs, basal ganglia Virchow-Robin spaces; CSO-VRs, centrum semiovale Virchow-Robin spaces; L-VRs, linear Virchow-Robin spaces; T1W, T1-weighted; FLASH, fast low-angle shot; TSE, turbo spin echo; SPIR, spectral presaturation with inversion recovery; IR-TSE, inversion recovery turbo spin echo; TW1 IR, T1-weighted inversion recovery; FSE, fast spin echo; SI, substantia innominata; FSE T2, fast spin echo T2; T2WI, T2-weighted imaging; T1W, T1-weighted imaging; PD, proton density; T2W, T2-weighted SE, T2-weighted spin echo; NA, not applicable

Table 8.2 Unweighted κ scores and proportional agreement for intrarater (A) and interrater agreement (B) in the centrum semiovale, basal ganglia and midbrain, using dichotomized enlarged perivascular spaces scores (0-2 vs 3-4) for centrum semiovale and basal ganglia regions

A.

	Intrarater agreement			
	Rater 1		Rater 2	
Region	Kappa (95% CI)	Proportional agreement (%, 95% CI)	Kappa (95% CI)	Proportional agreement (%, 95% CI)
Centrum semiovale	0.61 (0.51, 0.93)	80 (67.7, 89.2)	0.6 (0.4, 0.8)	80 (67.7, 89.2)
Basal ganglia	0.73 (0.56, 0.9)	86.7 (75.4, 94.1)	0.86 (0.72, 0.99)	93.3 (83.8, 98.2)
Midbrain	0.62 (0.32, 0.92)	91.7 (81.6, 97.2)	0.72 (0.51, 0.93)	90 (79.5, 96.2)

B.

	Interrater agreement			
	First rating		Repeat rating	
	Kappa (95% CI)	Proportional agreement (%, 95% CI)	Kappa (95% CI)	Proportional agreement (%, 95% CI)
Centrum semiovale	0.58 (0.39, 0.77)	95 (86.1, 99)	0.57 (0.36, 0.77)	78.3 (65.8, 87.9)
Basal ganglia	0.86 (0.73, 0.99)	93.3 (83.8, 98.2)	0.57 (0.36, 0.77)	83.3 (71.5, 91.7)
Midbrain	0.53 (0.13, 0.27)	85 (73.4, 92.9)	0.41 (0.12, 0.70)	83.3 (71.5, 91.7)

CI, confidence interval

Table 8.3 Details of cases causing disagreement for intrarater (A) and interrater (B) enlarged perivascular spaces (EPVS) variability testing

A.

Region	Description	n (%)
Centrum semiovale	Asymmetric/focally dilated EPVS	1 (5)
(n=20)	WMH present[a]	7 (35)
	No WMH present[b]	11 (55)
	Movement artefact	1 (5)
Basal ganglia (n=8)	Rating 2 vs 3, no clear cause for disagreement	6 (75)
	Unilateral TACI	1 (12.5)
	Multiple possible lacunes bilaterally	1 (12.5)

[a]1-point difference in scale, n=4; 2-point difference, n=2; 3-point difference, n=1; WMH confluent (n=5) or scattered (n=2)
[b]1-point difference in rating in 9/10 cases
WMH, white matter hyperintensities; TACI, total anterior circulation infarction

B.

Region	Description	n (%)
Centrum semiovale	WMH present[a]	9 (42.9)
(n=21)	No WMH present[b]	11 (52.4)
	Movement artefact	1 (4.8)
Basal ganglia (n=12)	Rating 2 vs 3, no clear cause for disagreement	5 (41.7)
	Unilateral TACI	1 (12.5)
	Multiple possible lacunes[c]	6 (50)

[a]1-point different in scale, n=6; 2-point difference, n=3; WMH confluent (n=7) or scattered (n=2)
[b]1-point difference in rating in 10/11 cases
[c]Unilateral in 3, bilateral in 3
WMH, white matter hyperintensities; TACI, total anterior circulation infarction

8.7 Figures

Figure 13 Examples of enlarged perivascular spaces (EPVS) on T2-weighted magnetic resonance imaging.

(A) Grade 4 enlarged perivascular space (EPVS) (>40 EPVS) in the frontal region in a magnified view of the centrum semiovale. (B) Grade 2 EPVS (11-20 EPVS) in the basal ganglia (arrowheads). (C) Visible (grade 1) midbrain EPVS (arrowheads).

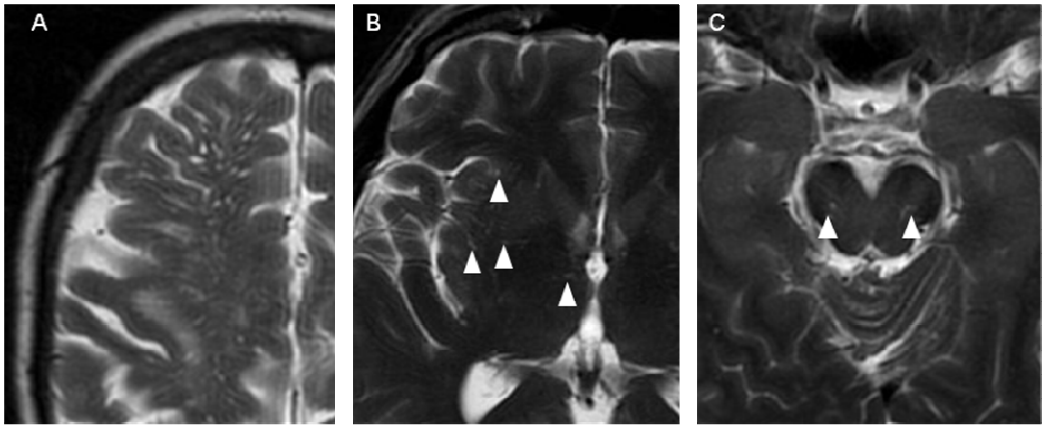
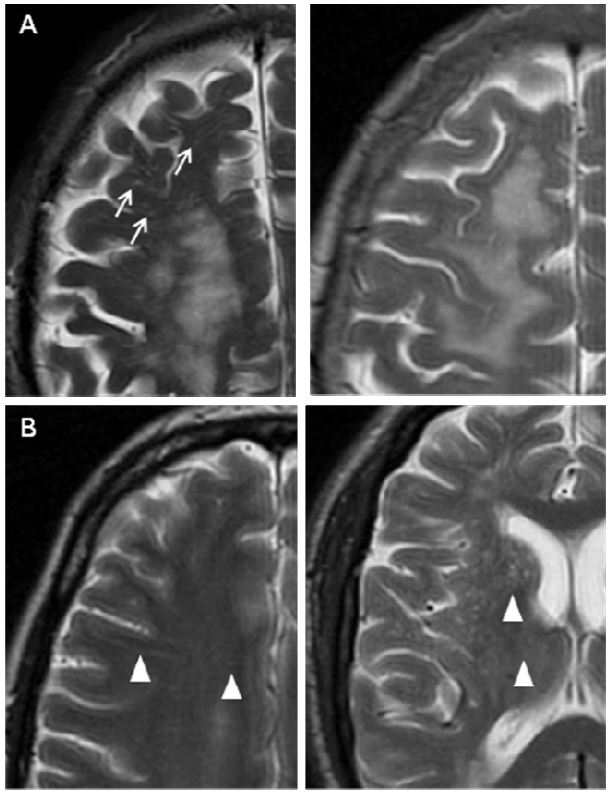


Figure 14 Main causes for observer variability in enlarged perivascular spaces (EPVS) rating

(A) Magnified view of white matter lesions in the right centrum semiovale, which may be scattered with EPVS still visible (left, arrows) or confluent, making EPVS rating difficult (right). (B) Small, poorly visualised EPVS in the centrum semiovale (left) and basal ganglia (right, arrowheads, with several adjacent EPVS which are clearly visible).



Chapter 9. Improving quantification of other features of cerebral small vessel disease: development of the Brain Observer MicroBleed Scale (BOMBS)

9.1 Introduction

In stroke medicine, the burning questions about BMB concern their diagnostic significance (for example, for the ante mortem diagnosis of cerebral amyloid angiopathy and other disorders), and whether BMB should influence the use of antithrombotic and thrombolytic drugs (Fiehler et al. 2007, Lovelock et al. 2010). If the diagnostic and prognostic significances of BMB are to be investigated and used for these purposes in clinical practice, then definitive research studies should fulfill a variety of prerequisites (Cordonnier et al. 2007), including knowledge of the effectiveness of the scales used to rate BMB as well as the intra- and interrater variation of the individual researchers using the scales.

Previous studies have reported variable levels of interrater agreement amongst two or three observers (Greenberg et al. 1999, Jeerakathil et al. 2004b, Jeon et al. 2007, Kakuda et al. 2005, Kwa et al. 1998, Lee et al. 2004, Lee et al. 2005b, Lee et al. 2006, Lee et al. 2007, Lemmens et al. 2007, Roob et al. 1999, Vernooj 2008,Viswanathan et al. 2006; Table 9.1). Studies of interrater reliability found kappa (κ) values ranging from 0.33 (fair; Jeerakathil et al. 2004b) to 0.88 (excellent; Jeon et al. 2007, Lee et al. 2004); most found $\kappa>0.7$, sample sizes were small, 95% CIs were not always provided, and the properties of the rating scales used were not described.

9.2. Aims

In view of the variation in reported interrater agreement in BMB, the potential for a rating scale to improve levels of agreement, and the absence of a rating scale for BMB, we further quantified interrater agreement about the presence, number, size, and location of BMB in order to develop a simple BMB classification scheme which might minimise observer variation.

9.3. Methods

9.3.1. Patient recruitment

We studied a subset of patients from the ESS (described above; Table 9.2). Consecutive consenting stroke and TIA patients were recruited to the register from outpatient clinics and hospital admissions. In the current study we included those patients who had undergone at least one MRI scan with GRE sequences (n=264). If a patient had more than one MRI, we used the earliest scan.

9.3.2. Brain imaging

Patients underwent brain MRI according to the ESS protocol as described above (Chapter 2, Table 2.1).

9.3.3. Brain microbleed rating

A neuroradiologist (GMP) and a neurologist (CC), both with experience in rating BMB, independently assessed all MRI sequences on hard copy imaging of 264 adults, using a

pilot BMB rating scale, which required the reader to quantify BMB sub-divided by size (<5mm, 5-10mm), side of brain (left, right), and location (lobar [cortex/grey-white junction; subcortical white matter], deep [BG grey matter; internal and external capsules; thalamus], and posterior fossa [brainstem; cerebellum]) (Figure 15). All BMB were measured manually. Each observer was blinded to clinical data and to the other observer's ratings. BMB were defined as homogeneous, round foci, <10mm diameter (no minimum size was specified), of low signal intensity on GRE MRI. The observers were aware of the main BMB mimics (Samarasekera et al. 2011). Low signal lesions on GRE MRI within a lesion compatible with an infarct were regarded as haemorrhagic transformation of infarct rather than BMB.

Following the assessment of interrater agreement with the pilot scale, a senior neuroradiologist (JMW) reviewed MRI scans about which the two observers disagreed in their BMB ratings. We developed the Brain Observer MicroBleed Scale (BOMBS) to account for some of the common sources of disagreement and other major problems encountered (Appendix 10). We re-evaluated agreement between the same two observers using BOMBS, in a different set of patients undergoing identical MRI sequences and parameters, to quantify BMB sub-divided by size, side of brain, and location (as before), but with the addition of a further subdivision into 'certain' and 'uncertain' BMB categories. The study population for the assessment of BOMBS was a series of 156 patients with stroke (different to the 264 in whom the pilot rating scale was tested), who had been recruited in the MSS (see above for details) and another stroke study requiring MRI (outpatients presenting more than 1 week after a mild stroke, in

whom CT scanning would not discriminate between ischaemic or haemorrhagic stroke, requiring MRI for stroke subtyping).

9.3.4. Analysis

We quantified observer agreement using the un-weighted κ statistic for nominal data (such as dichotomised presence versus absence of ≥1 BMB), analysed in any brain location and in separate brain areas (lobar, deep, and posterior fossa). When using BOMBS, we calculated κ for BMB rated 'certain', and for BMB rated 'certain' or 'uncertain'. Intraclass correlation coefficients were calculated for the overall numbers of BMB. When exploring interobserver reliability in measurements of BMB size, we restricted our analysis to MRI scans on which both raters had observed 'definite' BMB in the same brain location. All analyses were performed the Statistical Package for the Social Sciences Version 13 (SPSS Inc., Chicago, IL, USA), except CIs for κ which were calculated using Confidence Interval Analysis software (Bryant 2000).

9.4. Results

Agreement about the presence/absence of ≥1 BMB in any location in the brain was moderate (κ 0.44, 95% CI 0.32 to 0.56), but it appeared to be better in deep and posterior fossa locations, when compared to lobar areas (Table 9.1). Intraclass correlation coefficient for the overall number of BMB was of 0.91 (95% CI 0.88 to 0.93). The two observers disagreed about the presence of ≥1 BMB on 65 MRI scans. When these disagreements were reviewed by a third observer (JMW), most were found to occur where there was doubt about whether there was one BMB on a scan or none. The main

causes for disagreement were common BMB mimics such as vascular flow voids (cortical and perforator vessels), irregularly-shaped lesions, lesions too pale to be confident about them being a BMB, partial volume artifacts from the petrous temporal bone or orbit, and variable signal dropout (Figure 16).

We revised the pilot rating scale on the basis of the causes of the observed disagreements to develop the BOMBS (Appendix 10). Interrater agreement about the presence/absence of ≥1 BMB improved using BOMBS, when the analysis was restricted to 'certain' BMB, but remained similar to the pilot rating scale when considering 'certain' and 'uncertain' BMB (Table 9.2). No significant differences in interrater reliability were discernible between brain locations using BOMBS (Table 9.2). Intraclass correlation coefficient for the overall number of certain BMB was of 0.93 (95% CI 0.91 to 0.95). There were 27 definite BMB observed by both raters in the same brain location, 25 of which were rated in the same size category (93%, 95% CI 77 to 98); two BMB were considered to be ≥5 mm by observer A, but <5 mm by observer B.

9.5. Discussion

We have shown that the assessment of BMB on GRE MRI in patients with stroke and/or TIA is not straightforward using a simple pilot rating scale, with only moderate levels of interrater agreement comparable to previous studies. BOMBS (Appendix 10) improved interrater reliability when all brain locations were analysed together, and particularly in lobar locations, which had been identified in our pilot study as a difficult part of the brain to rate (Table 9.2). Although the consideration of BMB mimics is widely

recognised as being important, observer variation persists, even when mimics are carefully thought about during MR scan review. BOMBS had its main effect by differentiating 'certain' BMB from 'uncertain' BMB – uncertainty about BMB may be an important problem, because it applied to between one third and one half of BMB in this study (Table 9.2).

BMB maximum diameters in prior research have varied from 2-5mm, to ≤7mm and ≤10mm (Fiehler et al. 2007). In this study, we found few BMB >5mm in diameter, and we found only two disagreements about BMB size, but further studies are needed of observer agreement in BMB size categorisation and of the pathological substrates for BMB of varying sizes, in different patient populations.

We found good agreement about the total number of BMB. It is quite possible that the number of BMB may influence their prognostic significance (Fiehler et al. 2007), but this is not beyond doubt. On both these counts, continuing to collect the total number of BMB rated by any observer – rather than subdividing a rating scale into no/few/many BMB – will contribute to improving agreement about BMB number, as well as determining what the numerical thresholds for BMB prognostic/therapeutic significance are. Furthermore, studying observers' certainty in relation to their ratings of the presence/absence of BMB as well as the number and size of BMB seen, will help understand whether small/uncertain BMB are more likely to be counted in patients with multiple certain BMB than those with a solitary certain BMB or multiple uncertain BMB. Patterns of rater behavior were evident in our study (Table 9.2).

Although studies have described the interrater reliability of BMB ratings (Table 9.1), we sought to improve agreement as our primary objective. We used κ and our study design fulfilled the assumptions inherent in the κ statistic; the subjects under study and the observers were independent, and the categories in the scale were independent, mutually exclusive, and exhaustive (Cohen 1960). The design of BOMBS benefited from the lessons gleaned using the pilot scale and independent review of the scans about which the observers disagreed. This study also benefited from using consistent imaging parameters and the same range of sequences (including GRE in all), and blinding of each observer to the other's ratings.

The main weakness of this study was that these findings have not yet been validated in larger cohorts, in other disease groups, and amongst other observers; we encourage other researchers to do so, to explore the generalisability of BOMBS. The influence of practice effects in our observers cannot be ruled out, but prior even to their ratings using the pilot rating scale, both had experience of interpreting BMB on MRI. The prevalence of BMB appeared to drop when BOMBS was validated, which was likely to have been related to the patients whose MRI scans were used to test BOMBS being younger and having milder strokes than those whose MRIs were used for the pilot rating scale; a systematic review has found BMB prevalence to be lower in these groups (Cordonnier et al. 2007). An artifact of the κ statistic is that it is affected in complex ways by the prevalence of the abnormality under study, but a drop in BMB prevalence from 20-40% to 18-25% was unlikely to have significantly biased the observers or affected the properties of the κ statistic.

The BOMBS dichotomisation of BMB into 'certain' and 'uncertain' was intended to improve agreement about the existence of certain BMB. Prioritising the identification of certain BMB would result in improved specificity (at the expense of sensitivity), by identifying BMB more reliably, which could improve the internal and external validities of research projects and encourage more reliable identification of BMB should they become relevant in clinical practice. Investigators could also explore the robustness of their study findings using sensitivity analyses (by restricting analyses to either 'certain' BMB, or 'certain' and 'uncertain' BMB, which would improve sensitivity at the expense of specificity). This dichotomisation also permits the identification of a separate group of MRIs with 'uncertain' BMB to further understand why and how observers disagree about BMB and follow-up such patients to determine if these 'uncertain' BMB mature into 'certain' BMB.

Our findings should be regarded as a baseline measure of observer agreement for future studies using BOMBS. Further work on ways of improving observer agreement about BMB is needed, and training observers to recognise certain and uncertain BMB, as well as their mimics, is an obvious priority. BOMBS will also enable others to study agreement about BMB size, number, brain location, and diagnostic certainty, as well as exploring the influence of these factors on the diagnostic and prognostic utilities of BMB.

Because the clinical implications of BMB remain to be established, there is still an opportunity to improve the reliability of BMB assessments by the use (and further development) of the BOMBS rating scale, so that adequately-powered, well designed

studies will be able to answer the outstanding clinical concerns about the diagnostic and prognostic value of BMB, and whether they should influence the prescription of antiplatelet, anticoagulant, or thrombolytic drugs. The use of a standard scale for BMB is also essential for future studies, to enable comparisons and meta-analyses.

9.6. Tables

Table 9.1 Published studies of interrater agreement about brain microbleeds (BMB)

Study	Numbers of observers	Number of MRI scans	Type of population	Prevalence of BMB	Type of analysis	Statistical test used	Interobserver agreement (95% CI where available)
Lee et al. 2006	2	125	ICH	66%	Total number of BMB	Spearman correlation	0.81
Greenberg et al. 1999	2	32	Lobar ICH	NS	Total number of BMB	Intraclass correlation	0.97
Viswanathan et al. 2006	2	20	CADASIL	35%	Total number of BMB	Intraclass correlation	0.96
Lee et al. 2004	2	102	Stroke and HTN	65%	Grade of BMB (4 grades)	Kappa	0.88 (0.81 to 0.95)
Jeon et al. 2007	2	63	ICH	68%	Presence or absence of BMB	Kappa	0.88
Lee et al. 2005b	2	143	ICH vs control	97% vs 56%	NS	Kappa	0.87
Lee et al. 2005b	2	26	ICH	NS	NS	Kappa	0.86
Kakuda et al. 2005	2	70	Ischaemic stroke treated with IV t-PA	16%	Presence or absence of BMB	Kappa	0.77 (0.55 to 0.99)
Greenberg et al. 1999	2	15	Lobar ICH	NS	Presence or absence of new BMB	Kappa	0.73
Lemmens et al. 2007	2	342	TIA or ischaemic stroke	26%	Presence or absence of BMB	Kappa	0.71 (0.59 to 0.82)

Table 9.1 continued

Study	Numbers of observers	Number of MRI scans	Type of population	Prevalence of BMB	Type of analysis	Statistical test used	Interobserver agreement (95% CI where available)
Kwa et al. 1998	2	221	Mixed	14%	NS	Kappa	0.6
Roob et al. 1999	3	280	'Healthy'	6%	Presence or absence of BMB	Kappa	0.40 to 0.65
Jeerakathil et al. 2004b	3	222	'Healthy'	5%	Presence or absence of BMB	Kappa	0.33 to 0.57
Vernooij et al. 2008	2	300	'Healthy'	24%	Presence or absence of BMB	Kappa	0.85

MRI, magnetic resonance imaging; CI, confidence interval; ICH, intracerebral haemorrhage; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; HTN, hypertension; NS, not specified; IV t-PA, intravenous tissue plasminogen activator; TIA, transient ischaemic attack

Table 9.2 Characteristics of the study populations and interrater agreement (simple [unweighted] kappa statistic) about the presence of ≥1 brain microbleed (BMB) in separate brain areas or in any brain location using the pilot rating scale and using the Brain Observer MicroBleed Scale (BOMBS)

		Pilot population (n=264)			BOMBS population (n=156)					
Median age (IQR)		72 (60-78)			66 (56-75)					
Ischaemic stroke		235 (90%)			151 (97%)					
Intracerebral haemorrhage		10 (4%)			5 (3%)					
Transient ischaemic attack		15 (6%)			0					
History of stroke or transient ischaemic attack		79 (30%)			22 (14%)					
History of treated hypertension		135 (51%)			81 (52%)					
		Pilot rating scale			**BOMBS rating scale**					
					Certain & uncertain BMB			***Certain BMB***		
		Observer A	Observer B	Kappas 0 vs ≥1 BMB (95% CI)	Observer A	Observer B	Kappas 0 vs ≥1 BMB (95% CI)	Observer A	Observer B	Kappas 0 vs ≥1 BMB (95% CI)
All locations	Patients with ≥1 BMB (%; 95% CI)	105 40 (34 to 46)	54 20 (16 to 26)		28 18 (13 to 25)	39 25 (19 to 32)		18 12 (7 to 18)	21 14 (9 to 20)	
	Number of lesions on all scans	320	362	0.44 (0.32 to 0.56)	67	107	0.38 (0.19 to 0.57)	43	61	0.68 (0.49 to 0.86)
	Median number of lesions per patient (IQR)	1 (1 to 3)	2 (1 to 7.25)		2 (1 to 2)	1 (1 to 2.5)		1.5 (1 to 2)	2 (1 to 2.5)	
Lobar	Patients with ≥1 BMB (%; 95% CI)	71 27 (22 to 33)	39 15 (11 to 20)		16 10 (6 to 16)	24 15 (11 to 22)		12 8 (5 to 13)	13 8 (5 to 14)	
	Number of lesions on all scans	188	231	0.44 (0.30 to 0.58)	29	48	0.49 (0.26 to 0.71)	19	28	0.78 (0.60 to 0.97)
	Median number of lesions per patient (IQR)	1 (1 to 2)	2 (1 to 6.5)		1 (1 to 2)	1 (1 to 2)		1 (1 to 2)	1 (1 to 2)	

Table 9.2 continued

Deep	Patients with ≥1 BMB (%; 95% CI)	50 19 (15 to 24)	30 11 (8 to 16)		17 11 (7 to 17)	22 14 (10 to 20)		9 6 (3 to 11)	12 8 (5 to 13)	
	Number of lesions on all scans	95	88	0.62 (0.48 to 0.76)	28	43	0.39 (0.14 to 0.63)	18	19	0.54 (0.25 to 0.83)
	Median number of lesions per patient (IQR)	1 (1 to 2)	2 (1 to 4)		1 (1 to 1)	1 (1 to 2)		1 (1 to 1)	1 (1 to 1)	
Posterior fossa	Patients with ≥1 BMB (%; 95% CI)	23 9 (6 to 13)	18 7 (4 to 11)		5 3 (1 to 7)	6 4 (2 to 8)		3 2 (1 to 6)	6 4 (2 to 8)	
	Number of lesions on all scans	37	43	0.66 (0.47 to 0.84)	10	16	0.91 (0.72 to 1.00)	6	14	0.66 (0.28 to 1.00)
	Median number of lesions per patient (IQR)	1 (1 to 2)	2 (1 to 4)		1 (1 to 2)	1 (1 to 4)		1 (1 to 2.5)	1 (1 to 4)	

IQR, interquartile range; CI, confidence interval

9.7. Figures

Figure 15 Diagram to illustrate lobar and deep regions of brain superimposed on axial gradient echo MRI brain

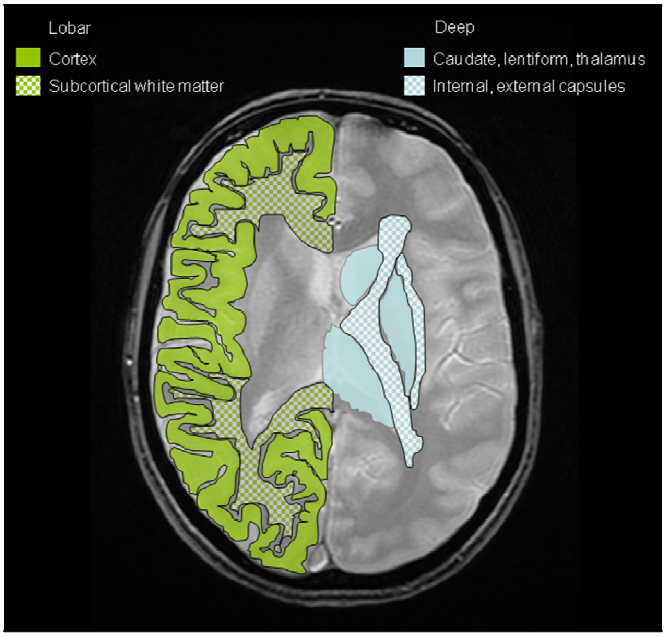
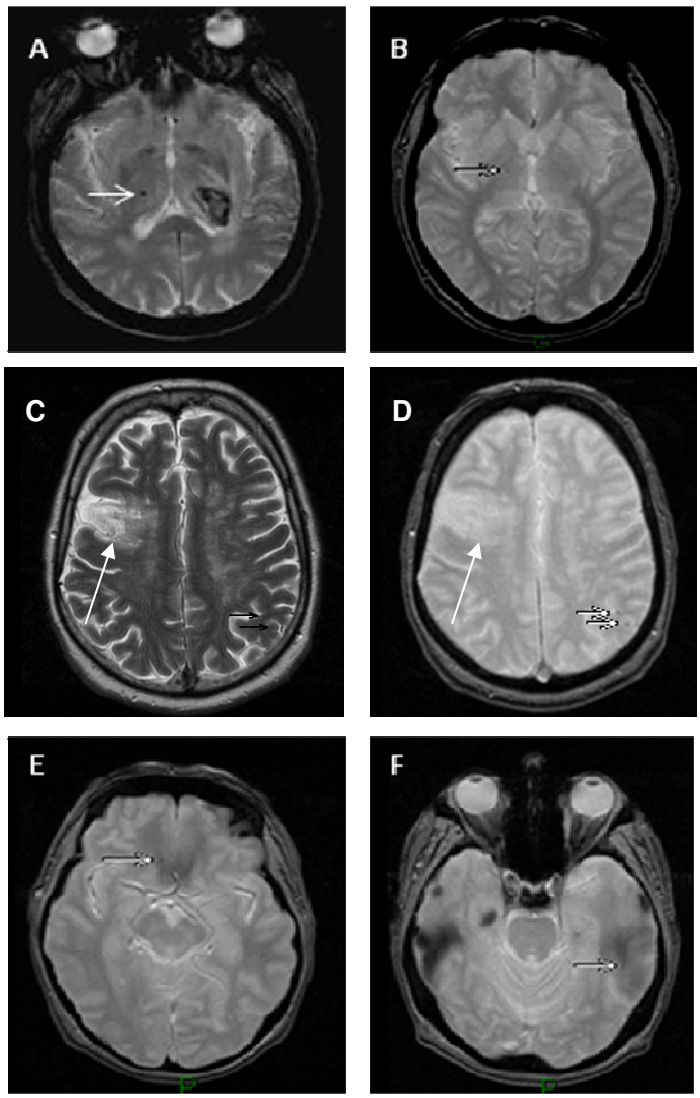


Figure 16 Examples of certain and uncertain brain microbleeds (BMB) and BMB mimics.

(A) Axial gradient echo (GRE) showing a certain BMB in the right thalamus (arrow). (B) Uncertain BMB, with a pale gray lesion in the right thalamus (arrow). (C) and (D) Small cortical vessels in the left parietal lobe (short arrows) on T2-weighted (C) and GRE imaging (D) mimicking BMB in a patient with an old right frontal cortical infarct (long arrows). (E) and (F) BMB mimics on GRE imaging due to partial volume artefact from right orbit (E) and left mastoid air cells (F) (arrows).



Chapter 10. Discussion

In my investigation of 'clinical-imaging dissociation' in acute ischaemic stroke, I found that 23% of patients presenting with a PACS had an acute lacunar infarct on MRI with DWI, and 16% of patients presenting with a LACS had an acute cortical infarct. In multivariate analysis adjusted for potential confounders, diabetes was the main factor associated with 'clinical-imaging dissociation'. In patients with an acute lacunar infarct on DWI, proximity of the lacunar infarct to the cortex, increasing age, diabetes and left hemisphere location were associated in multivariate analysis with 'clinical-imaging dissociation', but not lesion size, multiple acute infarcts, time to scanning, WML, brain atrophy or history of prior stroke.

In my analysis of the proportion of acute, symptomatic lacunar infarcts undergoing cavitation, a fifth of patients with acute lacunar ischaemic stroke showed definite lacunar infarct cavitation on follow-up imaging at a median of 227 days after onset of stroke; in a 'pure' subgroup with an infarct on baseline MRI with DWI and follow-up MRI, definite cavitation occurred in 15% of lacunar infarcts. Definite cavitation was associated with increasing time to follow-up imaging in univariate and multivariate analysis, but not with increasing age, stroke severity, lesion size or location, or other features of cerebral SVD, including presence of other lacunes at the time of baseline imaging.

I investigated completeness of reporting of lacunar lesions in the lacunar stroke literature and found marked variation in terminology and descriptions of imaging definitions of

lacunar lesions. An imaging definition was provided in 26 (60%) studies of acute, and 8 (40%) of old, lacunar lesions. Definitions were heterogeneous and often incomplete. The terms 'lacunar infarct' and 'lacunar stroke' were used for all types of lesion, whether acute and old, symptomatic or asymptomatic. A minority attempted to seek relevant prior symptoms for old lacunar lesions. Clinical terminology varied widely, with a clinical stroke definition being provided in only half of studies. Only a third of studies using MRI included DWI. Non-radiologists interpreted images in most cases.

I assessed definition and detection of lacunar lesions on imaging in an online survey of SVD researchers and found marked variation in definitions and descriptions of lacunar lesions, with marked variation in terminology when describing posterior fossa lesions. Most participants agreed on definitions for lacunar lesion site and for EPVS. There was wide variation in lesion recognition and classification. Cavitated lesions of any size were detected with the highest degree of confidence, but were described using multiple terms. Detection of non-cavitated lacunar infarcts in the presence of WML was limited, and differentiation of lacunes from EPVS was poor.

In my investigation of the relationship between carotid stenosis and ipsilateral WML, I found no association between carotid stenosis asymmetry and WML asymmetry, or between increasing degrees of carotid artery stenosis and ipsilateral hemispheric WML, either with or without adjustment for vascular risk factors. In both studies, WML were strongly associated with increasing age, in agreement with previous studies.

In my examination of clinical and imaging associations of EPVS in patients with acute ischaemic stroke, I found that total EPVS were associated with age and deep WML. BG-EPVS were associated with age, CS-EPVS, cerebral atrophy and lacunar stroke subtype.

In order to develop a visual rating scale for EPVS, I reviewed existing EPVS rating scales, identified omissions or ambiguities in each, and used this information to make improvements to one existing scale. I assessed observer variability of the revised scale in 60 MRI scans chosen to demonstrate a full range of EPVS frequencies and designed a user guide with further modifications to help avoid residual sources of observer variation. Two observers showed similar intrarater agreement for BG-, CS- and MB-EPVS, ranging from good to very good kappa values. Interrater agreement was moderate for CS- and MB-EPVS on both ratings, although very good for BG-EPVS on the initial rating. Disagreements were mainly due to the counting of very small, but just visible, EPVS, and the presence of background WML and lacunes (in the CS and BG regions, respectively).

Using a pilot rating scale for BMB (the Brain Observer MicroBleed Scale, BOMBS), I found that the assessment of BMB in patients with stroke and/or TIA is not straightforward, with only moderate levels of interrater agreement, comparable to previous studies. BOMBS improved interrater reliability when all brain locations were analysed together, and particularly in lobar locations, which had been identified in our pilot study as a difficult part of the brain to rate. BOMBS had its main effect by differentiating ‘certain’ BMB from ‘uncertain’ BMB. Observer variation persisted even when BMB mimics were considered during BMB rating.

There are strengths of this work. In several studies, we used patients from two large cohorts of ischaemic stroke patients recruited prospectively to an academic teaching hospital. In both studies, patients were carefully subtyped by a stroke physician, taking account of clinical syndrome and brain imaging, using the OCSP classification system. The use of large cohorts enabled us to assess several possible explanatory variables, where relevant, and to use multivariate analysis to correct for confounding factors. Patients had standard structural MRI brain imaging on the same scanner using the same protocol, which included GRE and DWI. ESS and MSS MRI scans were reviewed systematically according to a structured proforma, with assessment of SVD lesions according to detailed, pre-defined definitions and using all available sequences in order to distinguish as accurately as possible between the often overlapping features of SVD. MRI scans for each study (ESS, MSS) were assessed by independent raters blinded to all clinical details (except age and sex) and to each other's ratings. The neuroradiologist who rated the ESS MRI scans was aware at the time of rating of the hypothesis regarding influence of lacunar lesion site on clinical presentation, but was unaware of other hypotheses to be tested subsequently (WML vs carotid stenosis, EPVS associations, particularly the association with WMH and lacunar stroke subtype), thus eliminating evaluation bias. Rating scores for WML and EPVS were collected on a 'per hemisphere' as well as on a whole brain basis, and EPVS scores according to relevant major anatomical regions, enabling detailed analyses to be carried out. For assessment of lacunar infarct cavitation, we proposed our own definitions for 'partial' and 'definite' cavitation after careful assessment of imaging findings. Where possible, we used

validated scales in the image assessment proforma, enabling better cross-comparison with similar studies. In order to try and improve observer rating consistency, the less experienced rater was trained in WML and atrophy assessment using a test set of previously validated images, and provided with guidance on EPVS rating. Both raters carried out regular 'recalibration' during reading of images using the test set of images. In all patients who had carotid Doppler ultrasound, the examination was performed by dedicated neurovascular sonographers, with dual-reporting of stenoses measuring >50% NASCET, thus optimising consistency of assessment. In our studies assessing definitions of lacunar lesions, we assessed multiple aspects of definitions and terminology for different lesions types, including both clinical and radiological aspects, to enable a wider overall impression of potential problems relating to lacunar stroke research. We chose to survey interested experts in SVD disease in order to gain insight into current practice amongst relevant researchers. In our assessment of the relationship between carotid artery stenosis and WML, we overcame methodological limitations noted in previous studies. In designing new scales for rating EPVS and BMB, we used raters with previous experience in EPVS and BMB rating to allow informed modifications to both scales, and, recognising the inherent, commonly encountered difficulties in EPVS and BMB rating, designed a comprehensive user guide for each (both available online) as a potential aid to other interested researchers. For testing the revised EPVS scale, we deliberately selected images which demonstrated an appropriate range of severity/frequency of EPVS, and we fulfilled the assumptions inherent in the use of the κ statistic when testing each scale.

Limitations of this work include potential selection bias of patients in the ESS with an MRI. Although this subset was used in several studies, the potential influence of selection bias was most pertinent in our study of clinical-imaging dissociation, due to a possible overrepresentation of patients who were more difficult to subtype; however, this does not negate our observation that lacunar lesion location was associated with clinical-imaging dissociation. Additionally, median time from stroke onset to MRI was 19 days, i.e. outwith the time period considered optimal for DWI, and only 64% patients had a diffusion-positive infarct. However, a previous study showed that DWI may be useful up to several weeks after stroke onset (Keir et al. 2004). Images in the ESS and MSS were assessed by a single neuroradiologist on a single occasion, precluding assessment of intra- or interobserver reliability, which may have had a negative influence on the reliability of our results. However, we attempted to improve consistency in rating for WML by incorporating training on a test set of images demonstrating a full range of WML; for atrophy by using a validated scale including a template of images; and for EPVS by using a template of examples with rating instructions. Additionally, 'recalibration' was carried out by both raters during assessment of images, and raters used all sequences available in order to identify SVD features as accurately as possible, aware of areas of particular difficulty such as distinguishing EPVS from old, cavitated lacunes. In our study of lacunar lesion definitions, we collected a relatively small sample of data from the lacunar stroke literature; however, this does not negate our finding of marked variation in definitions of lacunar lesions and related methodologies, and variation is likely to have increased,

rather than decreased, with the inclusion of further articles. In our survey of imaging definitions and detection of lacunar lesions, only a third of those invited to participate took part, so our data represents only a fraction of opinions. However, most respondents were interested in SVD, therefore the responses received were probably sufficient to demonstrate the substantial lack of harmony for definitions used for, and generally poor detection of, lacunar lesions on imaging. The main limitation pertaining to our studies of observer agreement in rating EPVS and BMB is a lack of validation of our findings in larger cohorts, in other disease groups, and amongst other observers, including observers with less rating experience.

There are important implications of clinical-imaging dissociation, which has also been assessed in a recent study (Arboix et al. 2010), for research into epidemiology, pathophysiology and treatment of lacunar stroke. In research which relies heavily on clinical presentation alone, results may be affected by 'noise' caused by clinical-imaging dissociation of between 10 and 20% patients with mild stroke. Studies which do not use high sensitivity imaging - including those where MRI is used, but does not include DWI - are also likely to be affected. The effect on clinical-imaging dissociation of using imaging which is less sensitive (CT) and potentially more sensitive (Montiel et al. 2010) have not been assessed. The debate over mechanisms of lacunar stroke - up to 20% are said to be associated with cardiac and large artery atherothromboembolism (Davis and Donnan 2004, Futrell 2004, Kazui et al. 2001, Norrving 2004), rather than intrinsic SVD - could be explained by clinical-imaging dissociation. Large primary and secondary prevention trials of ischaemic stroke testing aspirin, cholesterol-lowering drugs and

antihypertensives, have relied heavily on clinical classification and CT (CAPRIE Steering Committee 1996); 'noise' from clinical-imaging dissociation may have impeded the demonstration of any difference in treatment effects between stroke subtypes, if one existed. Future epidemiology, pathophysiology and treatment of lacunar stroke should aim to subtype patients as accurately as possible.

Varied definitions and poor detection of lacunar lesions on imaging have important implications for all studies of cerebral SVD, including studies of lacunar stroke and WML. The overlapping appearances of lacunes and EPVS is well known (Román 2002), although in our literature review, only a minority of articles on lacunar stroke provided information on how the distinction between lacunar and EPVS was achieved; and when shown appropriate MRI sequences, SVD researchers mistook EPVS for lacunes, despite agreeing on an appropriate definition for EPVS. Less well-known is the significant problem of misclassification of non-cavitated symptomatic lacunar infarcts as WML. We found that only 1/5 of acute, symptomatic lacunar infarcts progressed to cavities. In our subsequent survey of researchers with an interest SVD, cavitated lacunar lesions of any size were detected with the highest degree of confidence, and detection of non-cavitated lacunar infarcts was poor, especially in the presence of other WML. In studies which only count lacunes as old lacunar infarcts (Romero et al. 2010, Srikanth et al. 2010, Vermeer 2007), the true burden of lacunar disease may be underestimated by as much as five times: up to 4/5 of symptomatic lacunar infarcts may resemble, and be misidentified as, WML at any time up to approximately five years after stroke, possibly longer. In all lacunar stroke and WML studies, misclassification of overlapping imaging

features may lead to detection of statistically significant associations where none exist, or to the failure to detect statistical associations where they do. The proportion of acute symptomatic lacunar infarcts undergoing cavitation should be confirmed in larger prospective studies of acute lacunar stroke using fixed, pre-determined follow-up time points. We found marked variation in imaging definitions for all types of lacunar lesion in the literature and amongst interested experts. Although similar problems have previously been demonstrated amongst neuropathologists (Pantoni et al. 2006), the extent of the problem in relation to the neuroimaging of cerebral SVD – both in the current literature, and amongst current SVD researchers (likely to be involved in publishing future SVD studies) - has, until now, not been clearly documented. Ideally, a consensus in the imaging definitions for all radiological markers of cerebral SVD should be reached by interested radiologists and clinicians. A set of representative images (e.g. of acute to old, partially to fully cavitated lacunar infarcts, lacunes, and other features of SVD, alone or in combination) could be provided, with definitions and descriptions made available for training purposes on relevant websites. A harmonised approach may help improve accuracy of results in all future cerebral SVD studies and to resolve some of the current controversies in the field of cerebral SVD, particularly with regard to the aetiology of lacunar stroke and WML. Current terms in common use (for which underlying aetiology and associations are often automatically assumed, e.g. 'lacunar infarction') may be better replaced by a more general term such as 'small vessel change' incorporating a purely radiological description of the lesion (using all MRI sequences, where relevant) including site/size and an indication as to whether there has been

correlation with relevant clinical symptoms. However, accurate clinico-radiological correlation can be problematic, even when medical records are available, and may be difficult to overcome. Furthermore, even with radiological training, some difficulties in accurate lesion classification may persist, such as differentiation of EPVS from small, cavitated lesions, particularly with CT alone; these may have to be accepted as an inherent limitation in the imaging assessment of cerebral SVD. Ultimately, a full appreciation of cerebral lesions in lacunar stroke can only be reached at the neuropathological level, although this is currently limited due to relatively low mortality in the acute stage of cerebral SVD, difficulties related to dissection of very small vessels, and the significant problem of attempting to correlate late-stage findings with clinical symptoms, if present. Newer approaches aiming at improving radiological-neuropathological correlation may help to partly overcome some of these (Grinberg et al. 2009).

The recognition of WML on cross sectional imaging in the last three decades, particularly on MRI, has led to a plethora of pathophysiology, epidemiology and pathophysiology studies of WML. We used standard structural MRI to investigate the relationship between WML and carotid stenosis, and found no association. Our results have also been substantiated in a recent similar study (Grüter et al. 2010). Existing data, including our data, would suggest that there is now substantial evidence that emboli have little role in the formation of WML (or, by association, with most lacunar ischaemic stroke) and that any suggestion of an association in previous studies between embolic sources (e.g. atrial fibrillation or carotid disease) and WML may simply have

been due to a third mediating factor, such as age or hypertension. Future studies should focus on determining what causes the intrinsic small vessel pathological changes that appear to underlie most WML. The role of newer imaging methods such as multiparametric (Muñoz Maniega et al. 2010) and multimodal (Nitkunen et al. 2008) MRI in the investigation of WML have yet to be fully determined. Direct visualisation of thrombus in small vessels on ultra high field MRI (Kloppenborg et al. 2010) may also help in unraveling the pathophysiology underlying cerebral SVD; however, the practicability and safety of this technique remains to be assessed. The totality of existing data would suggest that there is now substantial evidence that emboli have little role in the formation of WML (or by association, with most lacunar ischaemic stroke) and that any suggestion of an association in previous studies between embolic sources (e.g. atrial fibrillation or carotid disease) and WML may simply have been due to a third mediating factor, such as age or hypertension. Future studies should therefore focus on determining what causes the intrinsic small vessel pathological changes that appear to underlie most WML. There is growing evidence that cerebral SVD occurs in the context of a much broader vasculopathy (Thompson and Hakim 2009).

At present, the cause and associations of EPVS are unclear, but they may be part of the spectrum of SVD (Doubal et al. 2010). In our study, we found an association between total EPVS and WML, and between BG-EPVS and lacunar stroke, providing further evidence that EPVS may be a further imaging marker for cerebral SVD. Blood-brain barrier dysfunction may play a role in the aetiology of lacunar stroke (Wardlaw et al. 2009) and in patients with MS, in which EPVS become more visible with development

of active inflammation and subside again as inflammatory activity wanes (Wuerfel et al. 2008). EPVS are conduits for drainage of interstitial fluid from the brain (Abbott et al. 2004, Weller et al. 1992), so it is highly relevant if they alter in visibility with inflammation, given that SVD may have an inflammatory component. EPVS are also more frequent compared to healthy controls in CADASIL (Cumurciuc et al. 2006), where there is altered vessel wall permeability and extravasation of plasma proteins into the perivascular spaces (Poirier et al. 1983). It seems plausible that blood-brain barrier dysfunction may also play a role, as yet undefined, in the formation of EPVS. The use of EPVS as a surrogate marker for disease progression and in treatment trials has not yet been assessed. Recent work indicates that leakage of intravenously injected contrast into CSF predates progression of WML in patients with mild stroke (Valdés Hernández et al. 2010). Future studies should assess the association between leakage of contrast into the CSF with both EPVS severity and progression of EPVS severity in stroke patients, and with the development and progression of cavitation in acute, symptomatic lacunar infarction. Questions about the utility of EPVS for predicting future stroke, and for predicting progression of other imaging features of SVD (including EPVS themselves), remain unanswered. The association we found between EPVS and WMH/lacunar stroke subtype should be confirmed in larger studies.

BMB have also emerged as a potential radiological marker of cerebral SVD in recent years (Wardlaw et al. 2006, Cordonnier et al. 2007). At present, the pathophysiology, diagnostic and prognostic significance of BMB are unclear; one of the key questions about BMB, regarding whether presence of BMB should influence prescription of

antiplatelet, anticoagulant, or thrombolytic drugs, has recently been investigated (Lovelock et al. 2010). Reliable methods for assessing and rating imaging markers of cerebral SVD are essential to pathophysiology, diagnostic and prognostic studies. We developed new rating scales for both EPVS and BMB, and created a comprehensive user guide for each. A similar rating scale to BOMBS has recently been developed (Gregoire et al. 2009), in which BMB are categorised as 'certain' and 'uncertain' (as for BOMBS), but in which lobar BMB are also subdivided according to individual lobar anatomy. We are not aware of any other attempts to develop an EPVS rating scale at present. There is still an opportunity to improve the reliability of EPVS and BMB assessment by the use, and further development, of both rating scales. Further modifications to the EPVS rating scale should include additional ways to deal with very small EPVS and concomitant WML and lacunes. It is conceivable that further advances in MRI technology might lead to newer and better ways of identifying EPVS. The influence of variations in MRI parameters (Gregoire et al. 2010), and of use of more sensitive techniques such as susceptibility-weighted imaging (Wolf et al. 2010), on detection of BMB are beginning to be addressed. Our development of EPVS and BMB scales, and the further development of these, will hopefully act as a basis for all future studies of EPVS and BMB and enable better cross-comparison between studies. Training observers in how to rate EPVS and BMB should help to minimise observer variability and should be considered in all future EPVS and BMB studies.

In conclusion, neuroimaging is essential for investigating cerebral SVD. In this work, we highlight the need for sensitive cross sectional imaging in subtyping of patients with

acute ischaemic stroke; for a consensus approach to all imaging features of cerebral SVD, including EPVS and BMB; for appropriate training in the wide range of overlapping appearances of imaging markers of cerebral SVD; and the need for further studies in cerebral SVD, particularly those aimed at elucidating underlying pathophysiology. The rating scales we have developed for EPVS and BMB (features to emerge more recently as imaging markers of cerebral SVD) will hopefully act as a basis for future investigations of their diagnostic and prognostic significance. Neuroimaging has significant advantages over the once neuropathology-centred investigative approach to cerebral SVD: with ongoing technological advances, neuroimaging will remain an essential means of investigating cerebral SVD in the future.

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Appendices

Appendix 1. ESS clinical data collection forms (in-patient, out-patient)

Lothian Stroke Care Audit / ESS Form – Clinical Inpatient Information

Address label

Chi No. Sex

Unit No. WG

Name Title

Address

Date of admission : ____/____/____

Date of assessment : ____/____/____

Time of assessment: ____:____

Consultant in charge : _____

Final diagnosis and status (Please tick all that apply)

Cerebral[1]	Stroke (not SAH)	Transient ischaemic attack	Subarachnoid haemorrhage
Eye[1]	Retinal artery occlusion	Transient monocular blindness	
Other	Possibly cerebrovascular[2]	Details: _____	
	Definitely non-cerebrovascular	Details: _____	

Casemix assessment

Was the patient independent in ADL[3] before event ? [__] Are they oriented in time, place and person ? [__]

Was the patient living alone at the time of event ? [__] Can the patient lift both arms off the bed ? [__]

Can the patient talk[4] ? [__] Able to walk without help from another person ? [__]

NIH stroke scale score *(0-42; please complete scoring sheet on back page and see supplementary notes attached)* [_____]

Clinical assessment –presenting event(s) presenting event(s), past history & related signs

Date of onset of symptoms *(or best estimate)* ____/____/____

Time of onset of symptoms (enter ? if unknown)[5]

On aspirin at onset ? [__]

On other antiplatelet drug at onset ? [__]

On warfarin at onset? [__]

Side of brain/eye lesion *(please circle)*
Right / Left / Cerebellar or brainstem / Bilateral / Uncertain

Blood pressure at time of assessment [_____/_____]

Height (cm) [_____] *or* half - armspan[5] (cm) [_____]

Weight (to nearest kg) [_____]

Prior stroke (before presenting event(s)) ?[__]

Prior TIA (before presenting event(s)) ? [__]

History of ischaemic heart disease[6] ? [__]

History of treated hypertension ? [__]

History of diabetes mellitus ? [__]

Peripheral arterial disease[7] ? [__]

Cardiac failure[8] ? [__]

Clear history of atrial fibrillation ? [__]
(paroxysmal or persistent)

[1] Use these categories for **definite** or **probable** (>50% certain) cerebrovascular diagnoses
[2] Use if presentation could have cerebrovascular cause but < 50% certain and give details (e.g. lone vertigo)
[3] Independent in **walking**, **dressing**, **washing**, **feeding**, and **toileting**, not necessarily bathing, shopping or climbing stairs
[4] Able to utter understandable words even if quiet or slurred
[5] Mid-sternal notch to tip of middle finger with (non-paretic) arm outstretched at right angles to body and palm facing forward
[6] MI (including ECG evidence of silent MI) / angina /CABG/coronary angioplasty or stent etc
[7] History of claudication / rest pain / peripheral arterial intervention, or definite signs (absent foot pulses / femoral arterial bruit)
[8] Definite clinical signs of heart failure or taking at least two drugs for its treatment (eg. ACE-inhibitor and loop diuretic)

Codes for boxes [__]:	Yes	Y	Wider boxes are for numbers
	No	N	Please use ? for unknown
	Unknown	?	Dates: please use ?? for unknown, and complete what you can (e.g. ??/12/1980)
	Unassessable	=	

Clinical assessment - social and family history

Cigarette smoker ? *(please circle)* : Never / Ex>12 m / Current or ex<12 m / Unknown

If current or ex <12 m cigarette smoker, cigarettes / day ? [_____]

Alcohol intake (units/week) [_____]

1st degree relative with stroke / TIA ? [__] Mother / Father / Sibling(s) / Child(ren)
(please circle all that apply) :

If yes, how many 1st degree relatives in total? *(please circle)* : 1 / 2 / >2

1st degree relative with IHD / PAD[9] ? [__] Mother / Father / Sibling(s) / Child(ren)
(please circle all that apply):

If yes, how many 1st degree relatives in total? *(please circle)* : 1 / 2 / >2

Edinburgh Stroke Study information / consent

(if full consent already available following a previous event, simply write "CONSENT OBTAINED ALREADY" across this box)

Patient / relatives given info pack with consent form? [__]

Consent for ESS: Patient / Relative / Witnessed / Waiver / Refused / None yet
(please circle- see patient information sheet and consent forms for details)

Consent date: ____/____/____

Use of data for research purposes [__]

Blood for research [__]

Contact GP / examine medical records [__]

Follow-up [__]

Clinical classification of stroke / TIA syndrome[10] *(please circle)*: LACS / PACS / POCS / TACS / Eye[11] / Uncertain

Other risk factors or unusual cause of stroke or TIA ? [__] (circle any options that apply and give details)

coronary catheterisation / carotid endarterectomy / cardiac valve disease / haematological illness /

hereditary e.g. CADASIL / arterial dissection / coagulopathy / other

Details : _____

Clinical prediction of dependency at six months *(clinician's 'gut feeling' : 0-6 on Oxford Handicap scale[12])* [_____]

Assessing clinician *(please circle)*

MSD / RIL / PAGS / CPW / CLMS / BW / VC / Other *(please initial)* : _____

[9] ischaemic heart disease / peripheral arterial disease
[10] Based on clinical assessment *before* results of imaging or other investigations
[11] Use for transient monocular blindness / retinal artery occlusion
[12] Oxford Handicap Scale:
0 = no symptoms;
1 = minor symptoms which do not interfere with lifestyle;
2 = some restriction to lifestyle but look after themselves;
3 = significant restriction to lifestyle, preventing total independence;
4 = severe handicap preventing independent existence but not requiring constant attention;
5 = severe handicap, totally dependent, requiring attention night and day
6 = dead

Admission blood tests	Taken ? *(please tick)*	Date taken:	Result *(leave blank if not yet known)*	
FBC	☐	___/___/___	Haemoglobin (g/l)	[_____]
			Haematocrit (ratio)	[0●_____]
			White cell count (x 10^9/l)	[____●__]
			Platelets (x 10^9/l)	[_____]
ESR	☐	___/___/___	(mm/hour)	[_____]
U&E	☐	___/___/___	Urea (mmol/l)	[____●__]
			Creatinine (µmol/l)	[_____]
Glucose	☐	___/___/___	(mmol/l)	[____●__]
Lipids	☐	___/___/___	Total cholesterol (mmol/l)	[____●__]
			HDL cholesterol (mmol/l)	[____●__]
Research	☐	___/___/___		

Brain imaging and final classification

CT done ? [__] Date : ___/___/___ Evidence of new haemorrhage on CT/MRI[13] ?[__]

MRI done ? [__] Date : ___/___/___ Visible relevant infarct on CT/MRI ? [__]

Final syndrome classification : *(using all clinical and imaging information)* LACS / PACS / POCS / TACS / Uncertain / Eye[14]

Cardiac investigations

ECG since event available ? [__] AF on ECG ? [__] LVH on ECG[15] ? [__]

Echocardiogram done?*(please circle)*: None / TTE no contrast / TTE+contrast / TOE no contrast / TOE+contrast

Date of first echocardiogram : ___/___/___ LVH on echo ? [__]

Carotid imaging

Carotid Duplex examination performed ? [__] Date of 1st Duplex ___/___/___

2nd Carotid Duplex performed ? [__] Date of 2nd Duplex ___/___/___

MR Angiography performed ? [__] Date of MRA ___/___/___

CT Angiography performed ? [__] Date of CTA ___/___/___

Conventional Angiography performed ? [__] Date of angiography ___/___/___

Carotid imaging results	Right	Left
ICA % stenosis on Duplex[16] ?	[_____]	[_____]
Post-stenotic collapse (equivalent on Duplex) ?	[__]	[__]

Codes for boxes [__]:	Yes	Y	Wider boxes are for numbers
	No	N	Please use ? for unknown
	Unknown	?	Dates: please use ?? for unknown, and complete what you can (e.g. ??/12/1980)
	Unassessable	=	

[13] Include harmorrhagic transformation of infarct but **NOT** petechial haemorrhage / microbleeds

[14] Use for transient monocular blindness / retinal artery occlusion

[15] **Don't rely on automatic report.** Use voltage criteria – sum of S wave in V_1 or V_2 + R wave in V_5 or $V_6 \geq 3.5$ mV (35 mm)

[16] Record discrete figure or range. If >1 result, record most severe. If result 'normal' record 0%; if 'minor atheroma' record 30%.

Plaque instability / irregularity (on Duplex or MRA) ? [__] [__]

NIH Stroke Scale (Please circle the most appropriate response for each section. See supplementary notes attached. If untestable please state reason. Add the scores for each item to get the total, and do not count untestable items)		
1a Level of Consciousness (LOC)	0 1 2 3	Alert – *keenly responsive* Drowsy – *arousable by minor stimulation to obey, answer, or respond* Stuporous – *requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped)* Comatose – *responds only with reflex motor or autonomic effects or totally unresponsive*
1b LOC Questions	0 1 2	Answers both correctly Answers one correctly Incorrect Patient is asked to state the month & his/her age. No credit for partly correct answers.
1c LOC Commands	0 1 2	Obeys both correctly Obeys one correctly Incorrect Patient is asked to close & open eyes, grip & release normal hand
2. Best Gaze	0 1 2	Normal Partial gaze palsy – *gaze is abnormal in one or both eyes, no forced deviation/total gaze paresis* Forced deviation – *or total gaze paresis not overcome by oculocephalic manoeuvre*
3. Visual Fields	0 1 2 3	No visual loss Partial hemianopia or visual inattention Complete hemianopia Bilateral hemianopia – *including cortical blindness*
4. Facial Palsy	0 1 2 3	Normal Minor - *flattened nasolabial fold, asymmetry on smiling* Partial – *total or near total paralysis of lower face* Complete - *absent facial movement in upper and lower face on one or both sides*
5. Best Motor RIGHT ARM	0 1 2 3 4 x	No drift – *holds limb at 90 degrees for full 10 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement *Untestable (only for amputation or shoulder joint fusion – please state which)*
6. Best Motor LEFT ARM	0 1 2 3 4 x	No drift – *holds limb at 90 degrees for full 10 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement *Untestable (only for amputation or shoulder joint fusion – please state which)*
7. Best Motor RIGHT LEG	0 1 2 3 4 x	No drift – *holds limb at 45 degrees for full 5 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement *Untestable (only for amputation or hip joint fusion – please state which)*
8. Best Motor LEFT LEG	0 1 2 3 4 x	No drift – *holds limb at 45 degrees for full 5 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement *Untestable (only for amputation or hip joint fusion – please state which)*
9. Limb Ataxia	0 1 2 x	Absent Present in 1 limb Present in 2 or more limbs *Untestable (only for amputation or joint fusion – please state which)*
10. Sensory	0 1 2	Normal Partial loss - *patient feels pinprick is less sharp or is dull on affected side* Dense loss - *patient is unaware of being touched on face, arm, leg*
11. Best Language	0 1 2 3	No dysphasia Mild to moderate dysphasia - *obvious loss of fluency or comprehension, without significant limitation in ideas expressed or form of expression. Conversation about provided material difficult or impossible but examiner can identify items from patient's response.* Severe dysphasia - *all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener who carries burden of communication. Examiner cannot identify items provided from patient response.* Mute - *no usable speech or auditory comprehension.*
12. Dysarthria	0 1 2 x	Normal articulation Mild to moderate dysarthria - *patient slurs some words, can be understood with some difficulty.* Unintelligible or worse - *speech is so slurred as to be unintelligible (absence of or out of proportion to dysphasia) or is mute/anarthric* *Untestable (intubation or other physical barrier to producing speech – please state)*
13. Neglect	0 1 2	No neglect Partial neglect - *Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities* Complete neglect - *Profound hemi-inattention (e.g. does not recognise own hand or orients to only one side of space) or hemi-inattention to more than one sensory modality (e.g. visual + tactile).*

Codes for boxes [__]:				
	Yes	Y	Wider boxes are for numbers	
	No	N	Please use ? for unknown	
	Unknown	?	Dates: please use ?? for unknown, and	

Appendix 2 Outpatient data collection form

LOTHIAN STROKE CARE AUDIT / REGISTRATION FORM – Outpatients

Address label

Chi No. Sex

Unit No. WG

GP Initials_____ GP Surname_____

GP Postcode _____ GP Phone _____

Date of assessment ____/____/____

Responsible consultant _____ Unit : WGH

Date of referral ____/____/____ From GP ? [__]

Date referral received ____/____/____

Date of first appointment offered ____/____/____

Final diagnosis (of presenting event(s)) (Please tick all that apply)

Cerebral[1]	Stroke (not SAH) ☐	Transient ischaemic attack ☐	Subarachnoid haemorrhage ☐
Eye[1]	Retinal artery occlusion ☐	Transient monocular blindness ☐	
Other	Possibly cerebrovascular[2] ☐	Details: _____	
	Definitely non-cerebrovascular ☐	Details: _____	

Complete remainder of form only if definite / probable cerebrovascular diagnosis within last 6 months

Casemix assessment (complete for STROKE PATIENTS ONLY - refers to most recent event)

Was the patient independent in ADL[3] before event ? [__] Are they oriented in time, place and person ? [__]

Was the patient living alone at the time of event ? [__] Can the patient lift both arms off the bed ? [__]

Can the patient talk[4] ? [__] Able to walk without help from another person ? [__]

NIH stroke scale score *(0-42; please complete attached scoring sheet)* [_____]

Clinical assessment – presenting event(s), past history & related signs

Date of most recent stroke / TIA / eye attack ____/____/____ *(or best estimate)* Prior stroke - before presenting event(s) ? [__]

Number of TIAs (not strokes) in the last 3 months [_____] Prior TIA - before presenting event(s) ? [__]

Any stroke symptoms lasting > 7 days[5] ? [__] History of ischaemic heart disease[6] ? [__]

Side of brain/eye lesion *(please circle)* History of treated hypertension ? [__]

[1] Use these categories for **definite** or **probable** (>50% probability) cerebrovascular diagnoses within last 6 months

[2] Use and give details: if < 50% probability cerebrovascular cause (e.g. lone vertigo); or if presenting event(s) not within last 6/12

[3] Independent in **walking, dressing, washing, feeding,** and **toileting**, not necessarily bathing, shopping or climbing stairs

[4] Able to utter understandable words even if quiet or slurred

[5] Only count focal neurological symptoms. If too soon to be sure, please code as unassessable

[6] MI (including ECG evidence of silent MI) / angina /CABG/coronary angioplasty or stent etc.

Right / Left / Cerebellar or brainstem / Bilateral / Uncertain

Have there been carotid *and* vertebral events ?	[__]	History of diabetes mellitus ?	[__]
Residual neurological signs from presenting event(s) ?	[__]	Peripheral arterial disease[7] ?	[__]
Any symptomatic neck bruit ?	[__]	Cardiac failure[8] ?	[__]
Blood pressure	[_____/_____]	Clear history of atrial fibrillation ?	[__]
Height (cm)	[_____]		
Weight (to nearest kg)	[_____]		

Clinical assessment - social and family history

Cigarette smoker ? *(please circle)* : Never / Ex>12 m / Current or ex<12 m / Pipe or cigars only / Unknown

If current or ex <12 m cigarette smoker, cigarettes / day ? [_____]

Alcohol intake (units/week) [_____]

1st degree relative with stroke / TIA ? [__] Mother / Father / Sibling(s) / Child(ren)
(please circle all that apply) :

If yes, how many ? *(please circle)* : 1 / 2 / >2

1st degree relative with IHD / PAD[9] ? [__] Mother / Father / Sibling(s) / Child(ren)
(please circle all that apply):

If yes, how many ? *(please circle)* : 1 / 2 / >2

Data to audit use of 2[nry] preventative drugs
(for each column, please tick all that apply or confirm NONE at foot)

Use of following drugs :	At time of event for which referred	At time of first assessment	Recommended following NV assessment	**But** record if patient known not to tolerate
Aspirin	☐	☐	☐	☐
Dipyridamole (Persantin/Asasantin)	☐	☐	☐	☐
Clopidogrel (Plavix)	☐	☐	☐	☐
Warfarin	☐	☐	☐	☐
ACE inhibitor	☐	☐	☐	☐
Diuretic	☐	☐	☐	☐
Other antihypertensive	☐	☐	☐	☐

[7] History of claudication / rest pain / peripheral arterial intervention, or definite signs (absent foot pulses / femoral arterial bruit)
[8] Definite clinical signs of heart failure or taking at least two drugs for its treatment (eg. ACE-inhibitor and loop diuretic)

[9] ischaemic heart disease / peripheral arterial disease

Statin / lipid lowering agent	☐	☐	☐	☐
NONE	☐	☐	☐	n/a

Edinburgh Stroke Study consent

(if full consent already available following a previous event, simply write "CONSENT OBTAINED ALREADY" across this box)

Consent obtained for ESS ? *(please circle - see patient information sheet and consent forms for details)* Patient / Relative / Witnessed / None

Consent date : ____/____/____

Use of data for research purposes [__] Blood for research [__]

Contact GP / examine medical records [__] Follow-up [__]

Codes for boxes [__]:	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and complete what
	Unassessable	=	you can (e.g. ??/12/1980)

Blood tests	Done prior to clinic	Taken in clinic	Date blood taken:	Result *(leave blank if not yet known)*	
FBC	☐	☐	____/____/____	Haemoglobin (g/l)	[_____]
				Haematocrit (ratio)	[0●____]
				White cell count (x 10^9/l)	[____●__]
				Platelets (x 10^9/l)	[_____]
ESR	☐	☐	____/____/____	(mm/hour)	[_____]
U&E	☐	☐	____/____/____	Urea (mmol/l) [____●__]	
				Creatinine (µmol/l)	[_____]
Glucose	☐	☐	____/____/____	(mmol/l)	[____●__]
Lipids	☐	☐	____/____/____	Total cholesterol (mmol/l)	[____●__]
				HDL cholesterol (mmol/l)	[____●__]

Research[10]	☐	___/___/___
NONE[11]	☐	

Clinical classification of presenting stroke / TIA syndrome[12] *(please circle)*	LACS / PACS / POCS / TACS / Eye[13] / Uncertain

Other risk factors or unusual cause of stroke or TIA ? [__] (circle any options that apply and give details)
coronary catheterisation / carotid endarterectomy / cardiac valve disease / haematological illness / hereditary e.g. CADASIL / arterial dissection / coagulopathy / other
Details : _____

Clinical prediction of outcome *(clinician's 'gut feeling')*				
Probability of stroke (%)	at one year	[_____]	at five years	[_____]
Probability of vascular event (%) *(stroke, MI or vascular death)*	at one year	[_____]	at five years	[_____]
Dependency *(for **STROKE PATIENTS ONLY**)* *(0-6 on Oxford Handicap scale[14])*	at six months	[_____]		
Assessing clinician *(please circle)*	MSD / RIL / PAGS / CPW / CLMS / BW / Other *(please initial)* : _____			

[10] For research bloods, please fill completely: two normal 2.7 ml EDTA tubes (red top). Label with hospital patient stickies. Research samples should be kept in the ice box provided and will be sent to the Wellcome Trust Clinical Research Facility at the end of the clinic.
[11] Tick this box if no blood tests done since referral event(s)
[12] Based on clinical assessment *before* results of imaging / other tests. If patient presents with TIA *and* stroke, classify the stroke.
[13] Use for transient monocular blindness / retinal artery occlusion
[14] Oxford Handicap Scale: 0 = no symptoms;
1 = minor symptoms which do not interfere with lifestyle;
2 = some restriction to lifestyle but look after themselves;
3 = significant restriction to lifestyle, preventing total independence;
4 = severe handicap preventing independent existence but not requiring constant attention;
5 = severe handicap, totally dependent, requiring attention night and day
6 = dead

Codes for boxes [__]:	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and complete what you can (e.g. ??/12/1980)
	Unassessable	=	

Cardiac investigations

ECG since event available ? [__] AF on ECG ? [__]

LVH on ECG ? [__]

Echocardiogram done ?*(please circle)*: None / TTE no contrast / TTE+contrast / TOE no contrast / TOE+contrast

Date of first echocardiogram : ___/___/____ Patent foramen ovale on echo? [__]

LVH on echo ? [__]

Data to audit carotid intervention service

Carotid Duplex examination performed ?	[__]	Date of 1st Duplex	___/___/____
2nd Carotid Duplex performed ?	[__]	Date of 2nd Duplex	___/___/____
MR Angiography performed ?	[__]	Date of MRA	___/___/____
CT Angiography performed ?	[__]	Date of CTA	___/___/____
Conventional Angiography performed ?	[__]	Date of angiography	___/___/____
Referred to vascular surgeons/interventional radiologist ?	[__]	Date referred	___/___/____

If not referred, why ? (please circle reason): patient choice / clinically not worthwhile (doctors decision) / mutual agreement / not appropriate (no severe stenosis)

If referred – intervention considered *(please circle)*: surgery / angioplasty ± stent

Seen by surgeon / radiologist ?	[__]	Date seen	___/___/____
Intervention performed ?	[__]		
If yes Side *(please circle)* Right / Left / Both		Date of (first) procedure	___/___/____
Stroke within 30 days of intervention ?	[__]		
Other complication(s) of intervention ?	[__]	*(please specify)*	_____
Reviewed in NV clinic after intervention ?	[__]	Date reviewed	___/___/____

Carotid imaging results	*Right*	*Left*
ICA % stenosis on 1st Duplex[15] ?	[_____]	[_____]
Post-stenotic collapse (equivalent on Duplex) ?	[__]	[__]
Plaque instability / irregularity (on Duplex or MRA) ?	[__]	[__]

[14] Include harmorrhagic transformation of infarct but **NOT** petechial haemorrhage / microbleeds

[15] Use for transient monocular blindness / retinal artery occlusion

[16] **Don't rely on automatic report.** Use voltage criteria – sum of S wave in V_1 or V_2 + R wave in V_5 or V_6 ≥ 3.5 mV (35 mm)

[17] Record discrete figure or range. If >1 result, record most severe. If result 'normal' record 0%; if 'minor atheroma' record 30%.

Codes for boxes [__]:	Yes	Y	Wider boxes are for **numbers**
	No	N	Please use ? for unknown
	Unknown	?	**Dates**: please use ?? for unknown, and
	Unassessable	–	complete what you can (e.g. ??/12/1980)

Appendix 3. Edinburgh Stroke Study and Mild Stroke Study imaging classification

Patient ID: _____ Date/time of MRI: _____

Sequences done: DWI/T2/FLAIR/GRE/T1/other

Relevant lesion present (age and location) **Y**es/**N**o

Sequence on which lesion present: DWI **Y**es/**N**o FLAIR/T2 - **Y**es/**N**o
Side of brain: **L**eft/**R**ight

Lacunar (size, mm _____)	**MCA cortical**	**Other cortical**
Internal capsule □	Small temporal □	Anterior ACA □
Internal border zone □	Small parietal	Posterior ACA □
Centrum semiovale □	Basal ganglia □	Anterior PCA □
Extends to cortical margin □	Subcortical □	Posterior PCA □
Thalamus □	Anterior half peripheral MCA□	Anterior border zone□
Lentiform nucleus	Posterior half peripheral MCA	Posterior border zone □
Brainstem□		

Old lesion(s) present **Y**es/**N**o

	Lesion 1	Lesion 2	Lesion 3
Left/**R**ight	Side □	Side □	Side □
Lac/**C**ortical/**P**osterior	Location □	Location □	Location □
Infarct/**H**aemorrhage	Type □	Type □	Type □

White matter lesion (WML) rating

		Overall	Left	Right
Periventricular WML	Fazekas 0/1//2/3 □	□		
Deep WML	Fazekas 0/1//2/3 □	□		
	De Leeuw n <3mm	□	□	□
	De Leeuw n 3-10mm		□	□
	De Leeuw n ≥10mm	□	□	

Enlarged perivascular spaces Basal ganglia 0-4 Centrum semiovale 0-4

Atrophy Deep atrophy **N**one/**M**ild/**M**oderate/**S**evere
Superficial atrophy **N**one/**M**ild/**M**oderate/**S**evere

Appendix 4. Mild Stroke Study clinical data collection form

Patient name _____ DOB ___/___/___ Sex M □ F □

CN number _____ Date of assessment for study ___/___/___

PMH

TIA □
Stroke □ (left □/right □ /both □/infarct □/haem □/cortical □/lacunar □)
Ischaemic heart disease □ (angina □ /MI □/angioplasty □/CABG □)
Peripheral Vascular Disease (or symptoms of) □
Diabetes mellitus □ (diagnosed at presentation □)
Hypertension □ Atrial fibrillation □
Hyperlipidaemia □
LVSD □
Structural heart disease □

Social and family history

Family history of stroke □
Cigarette smoker □ (ex-<12 months □, ex >12 months □, never □)
Alcohol use □ Units per week _____Previous alcohol excess □
Independent prior to stroke □

Details of presenting stroke

Date and time of symptom onset ____/_____/_____ - ___.____
Duration of symptoms _____ days or persisting
Date patient seen by stroke service ____/____/____
Side of body/vision affected Left □ Right □
Weakness □ (face □, arm □, leg □)
Sensory abnormality □ (face □, arm □, leg □)
Posterior circulation symptoms □
Dysphasia □ Neglect □ Visual field loss □
Right □ Left □ Handed
NIHSS score at assessment _____ and estimated worst _____

Investigations at time of presenting stroke

Total cholesterol _____
Blood glucose _____
ECG - sinus □ Atrial fibrillation □ LVH □
Carotid Doppler/ MRA Left ICA stenosis _____% Right ICA stenosis _____%
Echocardiology abnormality □ If so, complete free text
Blood pressure ____/____ mmHg

Medications at time of stroke	**Medications at time of MRI permeability scan**
Aspirin □	Aspirin □
Dipyridamole □	Dipyridamole □
Clopidogrel □	Clopidogrel □
Warfarin □	Warfarin □
Diuretic □	Diuretic □
ACE inhibitor □	ACE inhibitor □
Angiotensin II R antagonist □	Angiotensin II R antagonist □
Beta blocker □	Beta blocker □
Other antihypertensive □	Other antihypertensive □
Oral hypoglycaemic □	Oral hypoglycaemic □
Insulin □	Insulin □
Statin □	Statin □
Other chol-lowering medication	Other chol-lowering medication □

Classification

Clinical classification	Lacunar □	Cortical □	
Imaging classification	Lacunar □	Cortical □	
Final clinical and imaging classification	Lacunar □	Cortical □	POCS □

Free text comments

Appendix 5. Data extraction form for reporting of lacunar-related lesions

Lacunar lesion definition

Date extracted/initials Database entry date/initials

Journal details

RefMan database ID Year
Volume/Issue/Page
Title
1st author Last author
Corresponding author
Corresponding author department/institution/city
Country Continent
Other departments in authorship Y/N
If yes, number/type: Neurology/stroke/medicine/neuroradiology/geriatrics/psychiatry/other

Article type Original article/correspondence/comment/case report/review/other

Radiologist(s) in authorship Y/N

If yes, type Neuroradiologist/general radiologist
If yes, number

Background

Conclusions

Subjects

Subject type Hospital/community/unclear
If hospital, IP or OP IP/OP/both/unclear
If community, type Healthy/diseased If diseased, type
Clinical stroke Y/N Type (first ever/recurrent, etc) stated Y/N
If yes, type First ever/recurrent
If clinical stroke, type: Stroke alone/stroke + dementia/stroke + cardiovascular/stroke + other
If dementia, type stated Y/N
If yes, type Vascular/Alzheimer's/other

Imaging-related data – readers

Number readers stated Y/N If yes, number
Blinding of readers stated Y/N
Type of readers stated Y/N
If yes, type Neuroradiologist/radiologist/neurologist/stroke phys/general phys/psychiatrist/other
If yes, grade stated Y/N
If yes, state

Clinical data

Clinical term(s) stated Y/N If yes, term(s) used
Clinical definition stated Y/N
If yes, clinical definition
Refs given* Y/N Refs only Y/N

Primary aim of paper wrt age of lacunar lesion

Acute/non-acute/both *(complete relevant sections below)*

Acute lacunar lesions relevant Y/N

Term(s) used
Imaging definition stated Y/N
If yes, imaging definition Refs given* Y/N If yes, refs only Y/N
Type of imaging CT/MRI/both If MRI, sequences stated in full Y/N
MRI, magnet strength stated Y/N If yes, magnet strength
If MRI, sequences done DWI/T1/T2/FLAIR/PD/GRE/other
If MRI, description of sequences used for diagnosis Y/N If yes, sequences used
Reference to MR signal/CT attenuation Y/N If yes, state
Sites stated Y/N If yes, state
Timing of scan wrt symptoms stated Y/N If yes, state
Size stated Y/N
Minimal size stated Y/N If yes, state mm
Maximum size stated Y/N If yes, state mm
Shape stated Y/N If yes, state

Non-acute lacunar lesions relevant **Y/N**

Term(s) used
Imaging definition stated Y/N If yes, imaging definition
Refs given* Y/N If yes, refs only Y/N
Type of imaging CT/MRI/both
If MRI, sequences stated in full Y/N
If MRI, magnet strength stated Y/N If yes, magnet strength
If MRI, sequences done DWI/T1/T2/FLAIR/PD/GRE/other
If MRI, description of sequences used for diagnosis Y/N
If yes, sequences used
Reference to MR signal/CT attenuation Y/N If yes, state
Sites stated Y/N
If yes, state
Relationship to symptoms stated Y/N
If yes, interval stated Y/N If yes, interval
Size stated Y/N
Minimal size stated Y/N If yes, state mm
Maximum size stated Y/N If yes, state mm
Shape stated Y/N If yes, state

EPVS

Distinction of lacunes from EPVS stated anywhere in paper Y/N
If yes, criteria stated Y/N If yes, state

References *(1st author/year/journal – add up to 3 for each)*

Clinical
Acute
Non-acute

Further comments

Appendix 6. Introductory email for online survey of lacunar definitions

Subject: Survey of imaging definitions of lacunar infarcts - Dr G Potter/Professor J Wardlaw, The University of Edinburgh

Dear all,

We are interested in finding out more about how people define and interpret the appearance of lacunar infarcts on CT and MR imaging. We are particularly interested in the views of those with a research interest in cerebral small vessel disease, but also those of other neurologists, stroke physicians and neuroradiologists, who may be involved in the clinical care of patients with lacunar stroke.

You have received this because you have published on some aspect of lacunar stroke, or possibly because you belong to a neurology, stroke physician, neuroradiology or other relevant organisation.

We hope you will take the 15 minutes to complete our survey, which includes 9 clinical cases with imaging. Please note that if you choose to participate, the survey needs to be completed in one session, as partially completed versions cannot be saved.

The information you provide to us is completely anonymous and goes automatically into a database for analysis. If you would like to receive the final results of the survey once available, please contact Dr Gillian Potter (gillian.potter@ed.ac.uk). Please note that the survey results may be presented at scientific meetings and/or submitted for publication in the scientific literature.

To complete the survey, please use the following link:
http://www.surveymonkey.com/s.aspx?sm=T8r6sLfC2HEaGAPNxNBIow_3d_3d.

Please submit your responses by *Friday 16th October, 2009.*

If you are aware of any colleagues who may also be interested in participating in this survey, we would be grateful if you could forward this information to them. If you have any other queries about the survey, please contact Dr Gillian Potter.

Thank you again for your participation.

Kind regards,

Dr Gillian Potter
Neuroradiology Specialist Registrar & Clinical Research Fellow, The University of Edinburgh

Professor Joanna Wardlaw
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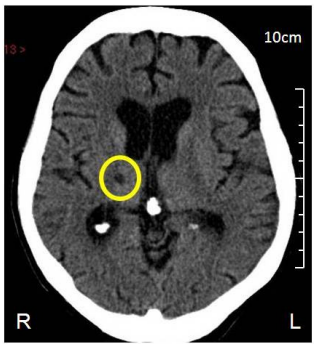
SINAPSE - Scottish Imaging Network, A Platform for Scientific Excellence (www.sinapse.ac.uk) - is a pooling initiative between the Universities of Aberdeen , Dundee, Edinburgh, Glasgow, St Andrews and Stirling, funded by the Scottish Funding Council and the Chief Scientist Office of the Scottish Government. GP is funded by the NHS Lothian R&D Office

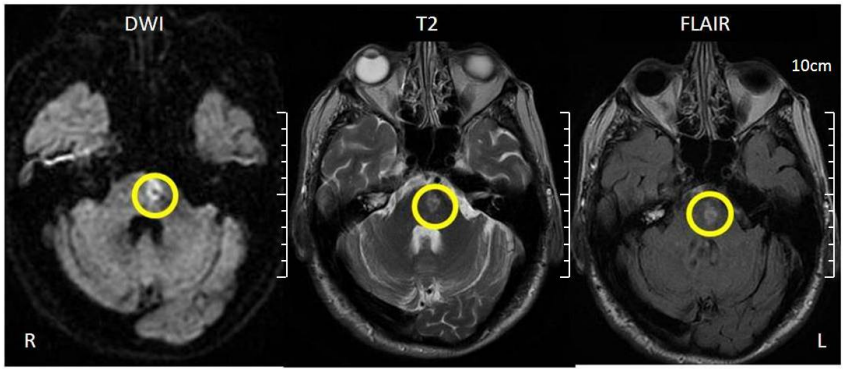
Appendix 7. Lacunar definition online survey: SurveyMonkey™ downloaded results

Case 1. Please indicate which term you consider most appropriate for the lesion circled in YELLOW in the right thalamus



1. Please indicate which term you consider most appropriate for the lesion circled in YELLOW in the right thalamus		Response Percent	Response Count
Lacunar infarct		44.6%	25
Lacunar stroke		5.4%	3
Subcortical infarct		5.4%	3
Subcortical stroke		0.0%	0
Small, deep infarct		7.1%	4
Small, deep stroke		5.4%	3
Lacune		25.0%	14
Black hole		5.4%	3
White matter lesion		1.8%	1
Other		0.0%	0
	If 'other', please specify/comment(s)		1
	answered question		56
	skipped question		2

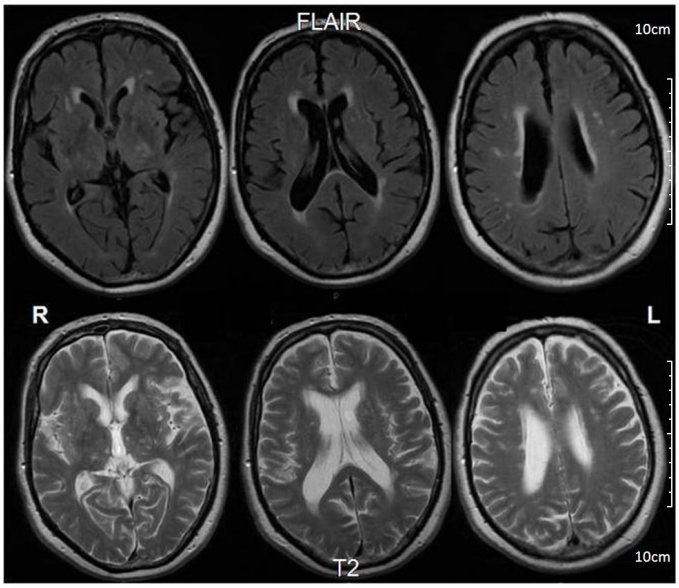
Case 2. Which term you consider most appropriate for this acute lesion?



2. Which term you consider most appropriate for this acute lesion?

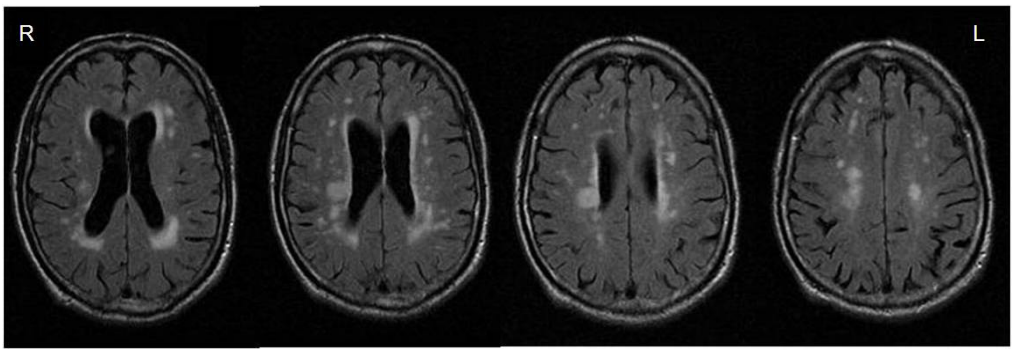
	Response Percent	Response Count
Lacunar infarct	41.1%	23
Lacunar stroke	1.8%	1
Subcortical infarct	1.8%	1
Subcortical stroke	1.8%	1
Small, deep infarct	16.1%	9
Small, deep stroke	0.0%	0
Lacune	0.0%	0
Black hole	1.8%	1
White matter lesion/white matter hyperintensity	0.0%	0
Other	35.7%	20
If 'other', please specify/comment(s)		21
answered question		56
skipped question		2

Case 3. Is there any evidence of an acute lacunar infarction in the LEFT hemisphere? (DWI/ADC – diffusion restriction internal capsule/corona radiata)



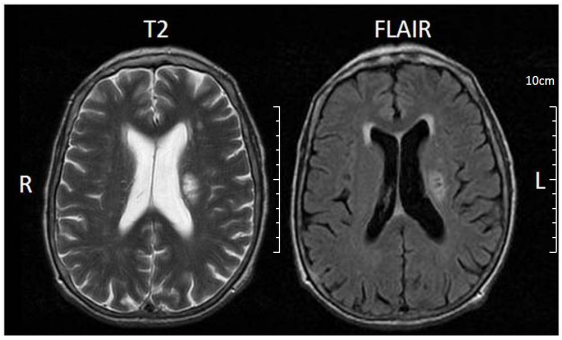
3. Is there any evidence of an acute lacunar infarction in the LEFT hemisphere?	Response Percent	Response Count
Yes, definitely	1.8%	1
Yes, probably	12.7%	7
Yes, possibly	18.2%	10
No	10.9%	6
Can't say without DWI	56.4%	31
answered question		55
skipped question		3

Case 4. Is there a lesion in the RIGHT cerebral hemisphere consistent with a lacunar infarct 2 years previously?



9. Is there a lesion in the RIGHT cerebral hemisphere consistent with a lacunar infarct 2 years previously?			
		Response Percent	Response Count
Yes, definitely		7.8%	4
Yes, probably		25.5%	13
Yes, possibly		33.3%	17
No		33.3%	17
	answered question		51
	skipped question		7

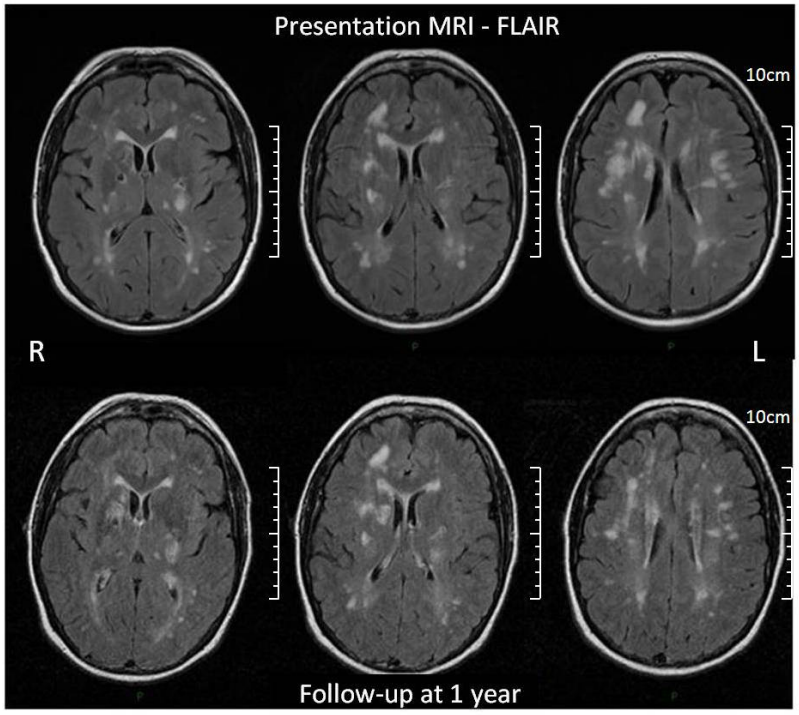
Case 5. Is there a lesion in the left hemisphere consistent with a lacunar infarct 18 months previously?



15. Is there a lesion in the left hemisphere consistent with a lacunar infarct 18 months previously?

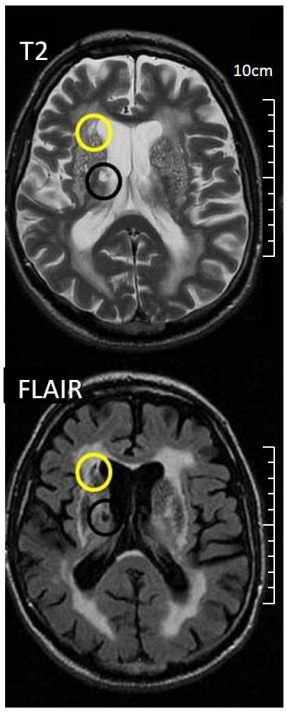
	Response Percent	Response Count
Yes, definitely	66.0%	33
Yes, probably	26.0%	13
Yes, possibly	4.0%	2
No	4.0%	2
answered question		50
skipped question		8

Case 6. Is there a lesion in the LEFT cerebral hemisphere of the bottom row of scans consistent with a lacunar infarct 12 months previously?



21. Is there a lesion in the LEFT cerebral hemisphere of the bottom row of scans consistent with a lacunar infarct 12 months previously?		
	Response Percent	Response Count
Yes, definitely	14.6%	7
Yes, probably	37.5%	18
Yes, possibly	37.5%	18
No	10.4%	5
answered question		48
skipped question		10

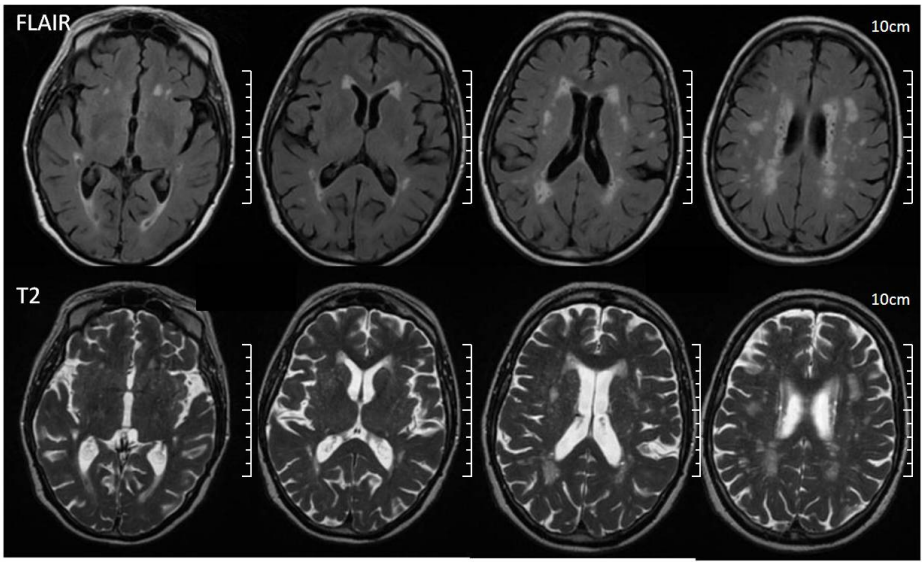
Cases 7 and 8. Which term do you consider most appropriate for the lesion circled in YELLOW and BLACK?



27. Which term do you consider most appropriate for the lesion circled in YELLOW?	Response Percent	Response Count
Lacunar infarct	**19.1%**	**9**
Lacunar stroke	0.0%	0
Subcortical infarct	2.1%	1
Subcortical stroke	4.3%	2
Small, deep infarct	6.4%	3
Small, deep stroke	6.4%	3
Lacune	**19.1%**	**9**
Black hole	12.8%	6
Virchow-Robin/perivascular space	14.9%	7
Uncertain	14.9%	7
Comment(s)		1
answered question		**47**
skipped question		**11**

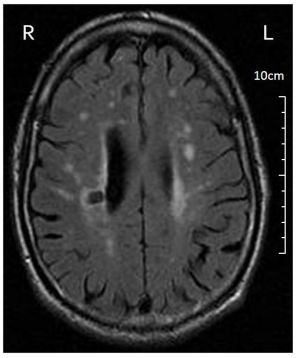
28. Which term do you consider most appropriate for the lesion circled in BLACK?	Response Percent	Response Count
Lacunar infarct	**40.4%**	**19**
Lacunar stroke	2.1%	1
Subcortical infarct	0.0%	0
Subcortical stroke	2.1%	1
Small, deep infarct	6.4%	3
Small, deep stroke	6.4%	3
Lacune	19.1%	9
Black hole	6.4%	3
Virchow-Robin/perivascular space	6.4%	3
Uncertain	10.6%	5
Other (please specify)/comment(s)		1
answered question		**47**
skipped question		**11**

Case 9. How many lacunes are visible?



29. How many lacunes are visible?		Response Percent	Response Count
0		21.3%	10
1		12.8%	6
2		6.4%	3
3		4.3%	2
4		8.5%	4
5		2.1%	1
>5		**44.7%**	**21**
	Comment(s)		10
	answered question		**47**
	skipped question		**11**

Case 10. Is there a lesion in the right hemisphere consistent with a lacunar infarct 18 months previously?



30. Is there a lesion in the right hemisphere consistent with a lacunar infarct 18 months previously?		
	Response Percent	Response Count
Yes, definitely	63.0%	29
Yes, probably	26.1%	12
Yes, possibly	8.7%	4
No	2.2%	1
answered question		46
skipped question		12

Question 11. Size definitions for lacunar lesions

36. What do you consider the best definition of SIZE of the following 3 lacunar lesions?						
	3-15mm	3-20mm	3-25mm	Unsure	Other	Response Count
ACUTE lacunar infarct	29.5% (13)	**38.6% (17)**	20.5% (9)	9.1% (4)	2.3% (1)	44
CHRONIC lacunar infarct	**61.4% (27)**	27.3% (12)	2.3% (1)	6.8% (3)	2.3% (1)	44
LACUNE	**55.8% (24)**	20.9% (9)	2.3% (1)	16.3% (7)	4.7% (2)	43
Other (please specify)/comment(s)						4
	answered question					**44**
	skipped question					**14**

Question 12. Definitions of site for lacunar lesions

37. What do you consider the best definition regarding SITE of lacunar lesions?	Response Percent	Response Count
Territory of deep perforating arteries - brainstem, basal ganglia (caudate nucleus, lentiform nucleus, internal capsule, thalamus) and white matter (corona radiata, centrum semiovale)	**97.7%**	**43**
Subcortical MCA territory	0.0%	0
Clinically relevant areas	0.0%	0
Deep white matter of brain and/or brainstem	2.3%	1
Deep in the brain	0.0%	0
Other (please specify)/comment(s)		5
answered question		44
skipped question		14

Question 13. Definitions for enlarged perivascular spaces

38. What do you consider the best definition of Virchow-Robin/enlarged perivascular spaces?	Response Percent	Response Count
≤2mm, round or linear lesions along the course of penetrating arteries with intensity close to CSF	15.9%	7
≤2mm, round or linear lesions at point of entry of MCA lenticulostriate arteries into basal ganglia, with intensity close to CSF	9.1%	4
Small, round or linear lesions along the course of penetrating arteries, with intensity close to CSF	**61.4%**	**27**
Small, round or linear, lesions at point of entry of MCA lenticulostriate arteries into basal ganglia, with intensity close to CSF	11.4%	5
Uncertain	2.3%	1
Other (please specify)/comment(s)		0
answered question		44
skipped question		14

Question 14. Participant discipline

39. Please inidicate which of the following most closely describes your main discipline:		
	Response Percent	Response Count
Neurologist	54.5%	24
Stroke physician	27.3%	12
General physician	0.0%	0
Care of the elderly physician	2.3%	1
Psychiatrist	0.0%	0
Old age psychiatrist	0.0%	0
General radiologist	0.0%	0
Neuroradiologist	13.6%	6
Other (please specify)	2.3%	1
answered question		44
skipped question		14

Question 15. Research interest in small vessel disease

40. Do you/your group have a research interest in cerebral small vessel disease?		
	Response Percent	Response Count
Yes	93.2%	41
No	6.8%	3
Comment(s)		2
answered question		44
skipped question		14

Question 16. Publications on lacunar infarction

41. Have you ever published scientific papers on lacunar infarction?		
	Response Percent	Response Count
Yes	84.1%	37
No	15.9%	7
answered question		44
skipped question		14

42. If you HAVE published on lacunar infarction, was a radiologist (general or neuroradiologist) involved in reading the images?		
	Response Percent	Response Count
Yes	73.0%	27
No	24.3%	9
Uncertain	2.7%	1
answered question		37
skipped question		21

Appendix 8. Enlarged perivascular spaces rating scale

	Rating	Number of EPVS	Description
Basal ganglia and centrum semiovale	0	No EPVS	None
	1	1-10 EPVS	Mild
	2	11-20 EPVS	Moderate
	3	21-40 EPVS	Frequent
	4	>40 EPVS	Severe
Midbrain	0	No EPVS visible	Absent
	1	EPVS visible	Present

Notes:

Review both sides of the brain for EPVS, but use the *highest number from 1 side only*

Review all relevant slices, but use the slice with the highest number of EPVS

In cases where rating is difficult (e.g. due to movement, extensive WMH or uncertainty due to variations in EPVS visibility), select the closest category

In cases of marked asymmetry (rare), record the score for the side of the brain with more EPVS

For basal ganglia EPVS, do not include EPVS in the anterior perforated substance

Appendix 9. Enlarged perivascular spaces rating scale user guide

Available at: http://www.sbirc.ed.ac.uk/documents/epvs-rating-scale-user-guide.pdf

Enlarged perivascular spaces (EPVS): a visual rating scale and user guide

Gillian Potter, Zoe Morris & Joanna Wardlaw

Section 1. Introduction

Enlarged perivascular spaces (EPVS, sometimes called Virchow-Robin spaces) surround the walls of vessels as they course from the subarachnoid space through the brain parenchyma.[1] EPVS appear in all age groups, but are only visualised clearly on T2-weighted brain magnetic resonance imaging (MRI) when enlarged.

Several EPVS rating scales have been described,[2-7] but these are either limited in their anatomical location, in the range of EPVS that they describe, or in their method of assessing severity. Additionally, some scales were tested using specific MRI sequences rather than standard structural brain MRI. We reviewed existing EPVS visual rating scales,[2-8] identified omissions or ambiguities in each, and used this combined knowledge to design improvements to one existing scale[8] that already most closely met requirements for a comprehensive easy to use scale. We then tested this revised scale on 60 MRI scans chosen to demonstrate a full range of EPVS frequencies and designed a comprehensive user guide. Using the revised scale and the user guide, two observers showed similar intra-rater agreement for BG-, CS- and midbrain EPVS ranging from good to very good kappa values. Inter-rater agreement was moderate for CS- and MB-EPVS on both ratings although very good for BG-EPVS on the initial rating. Disagreements were mainly due to the counting of very small but just visible EPVS, which were a recognised source of difficulty prior to rating. Other main causes for disagreement were the presence of background white matter hyperintensities (WMH), particularly when confluent, and lacunes (in the CS and BG regions, respectively). The user guide was subsequently modified to help avoid residual sources of observer variation.

This revised EPVS rating scale includes the 3 major anatomical regions where EPVS are found: basal ganglia (BG), centrum semiovale (CS) and midbrain.[1] The development of a validated rating scale, including a user guide with illustrations, will hopefully minimise interobserver variation in studies of EPVS, enable cross-comparison between research groups and facilitate meta-analysis of EPVS studies.

Section 2. EPVS on brain MRI

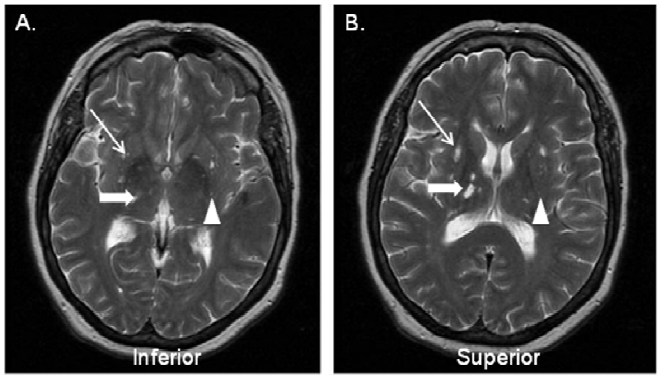
A. Definition

EPVS may be defined on MRI as 'small, sharply delineated structures of cerebrospinal fluid (CSF) intensity (or close to CSF intensity) measuring <3mm following the course of perforating vessels'.

B. Visualisation of EPVS on MRI

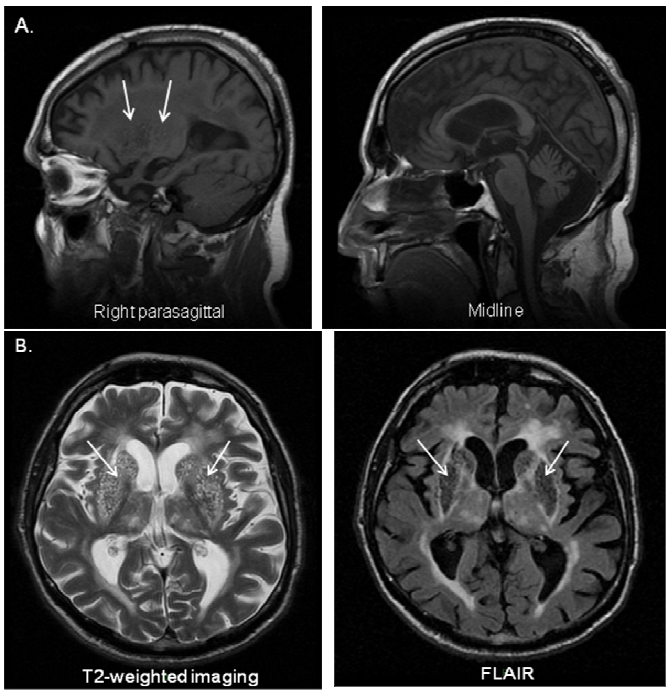
EPVS are most easily seen on T2-weighted imaging (T2WI), and may be distinguished from cavitated lacunes which contain CSF by the latter's large size (>3mm) and shape (spheroid; Fig 1); these features are often easier to see by reviewing adjacent slices.

Figure 1. Differentiating true EPVS (arrowhead) from lacunes containing CSF (thin and block arrows) in the basal ganglia using size and shape criteria



Although often described as hypointense structures on T1 and FLAIR, many EPVS will not be visible unless severe (Fig 2).

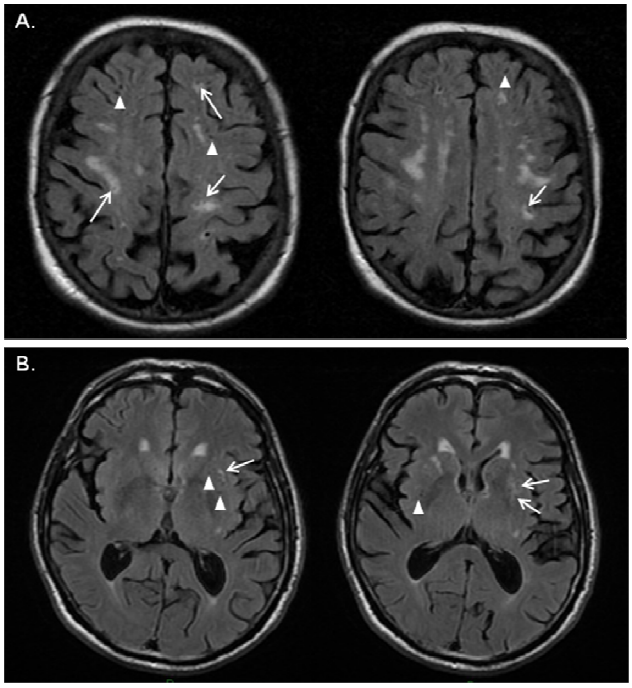
Figure 2. A. Sagittal T1 imaging showing severe EPVS in the basal ganglia (arrows). B. Axial T2 and equivalent FLAIR imaging showing a 'spongiform' appearance of the basal ganglia on both sides due to numerous EPVS



If EPVS are not identified on T2 images, it is very unlikely that they will be identified on other routine sequences. Thus, T2 images should always be reviewed first.

Although others have excluded EPVS with surrounding FLAIR hyperintensity when rating EPVS (Fig 3), these have been included in the current scale

Figure 3. Axial FLAIR MRI showing EPVS surrounded by white matter hyperintensities (WMH) in the centrum semiovale (A, arrows) and basal ganglia (B, arrows; different patient to A). EPVS without surrounding WMH are also visible in both regions (arrowheads).



C. Location of EPVS

EPVS are found throughout the brain, and are subpial spaces surrounding the perforating arteries, arterioles, veins and venules of the brain.

For EPVS rating, there are three primary areas to be considered: basal ganglia, centrum semiovale and midbrain. EPVS in these areas have been kept separate in the rating scale as it is possible that they may have different underlying pathophysiology.

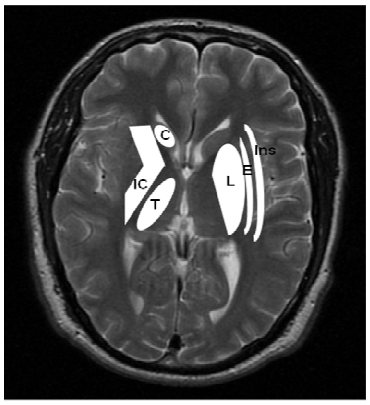
For the basal ganglia, this will normally involve reviewing at least 3 slices, for the midbrain, 1- 2, and for the centrum semiovale, at least 3 slices.

Each anatomical area will now be described in more detail.

Description of EPVS in each anatomical area

a. Basal ganglia EPVS

EPVS are seen in the basal ganglia along the paths of the perforating lenticulostriate arteries (arising from the middle cerebral artery), which enter the brain parenchyma inferiorly through the anterior perforated substance at the level of the anterior commissure, before coursing superiorly through the basal ganglia. However, EPVS in relation to perforating arteries in the insular cortex should be included in the basal ganglia EPVS rating. Structures to be reviewed in basal ganglia rating are shown in the following diagram:



C	Caudate nucleus
IC	Internal capsule
T	Thalamus
L	Lentiform nucleus
E	External/extreme capsules
Ins	Insular cortex

On standard axial T2MR imaging, EPVS in the basal ganglia most commonly appear as rounded foci of high signal (Fig 4). In the insular cortex, EPVS often appear as short linear structures due to different orientation of vessels (Fig 5).

Figure 4. Basal ganglia EPVS appearing as multiple, rounded, sharply delineated foci of T2 high signal (arrowheads)

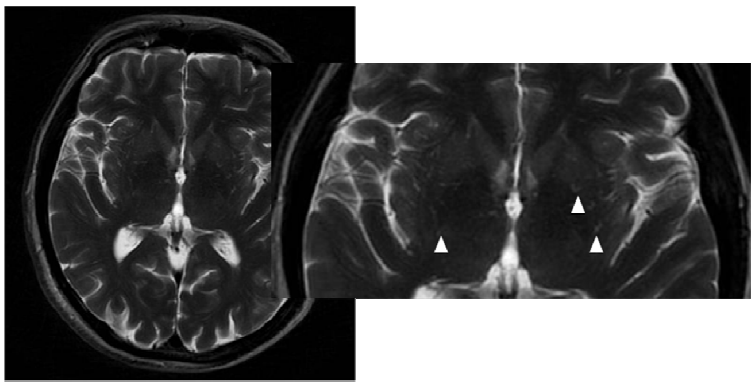
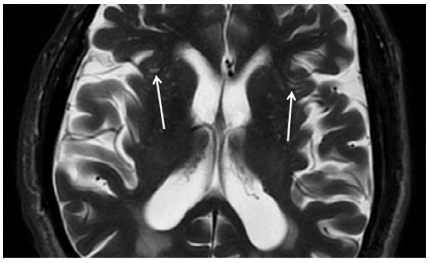
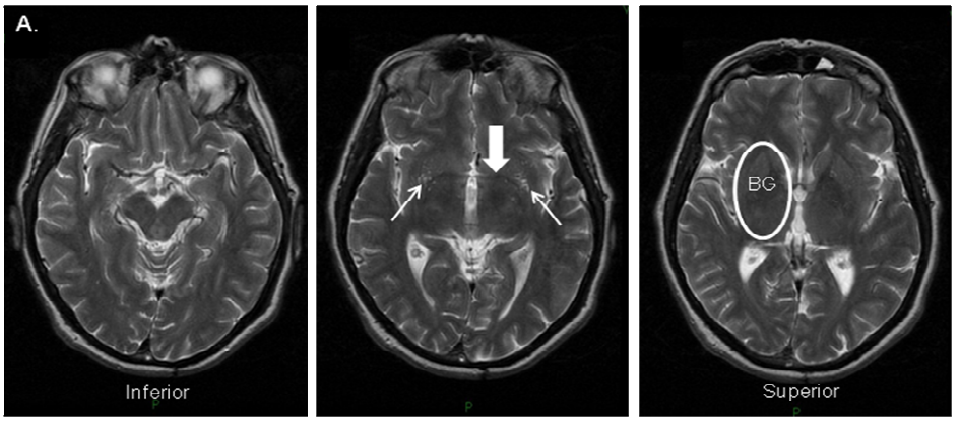


Figure 5. Linear EPVS following the course of perforating arteries in the insular cortex (arrows)

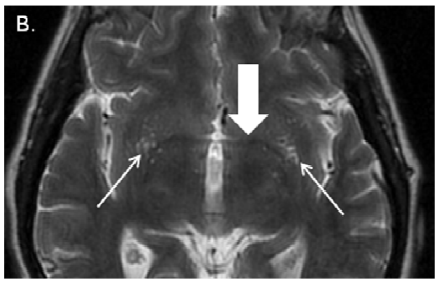


Inferior to the basal ganglia, at the level of the anterior perforated substance (or substantia innominata) most normal people will demonstrate EPVS (Fig 6). Rating of EPVS in the basal ganglia should therefore be done above this level: EPVS at the level of the anterior commissure should be excluded from the overall rating.

Figure 6. A. EPVS at the level of the anterior perforated substance (thin arrows), on the slice immediately above the upper midbrain (left image), and below the basal ganglia (circled, right image)



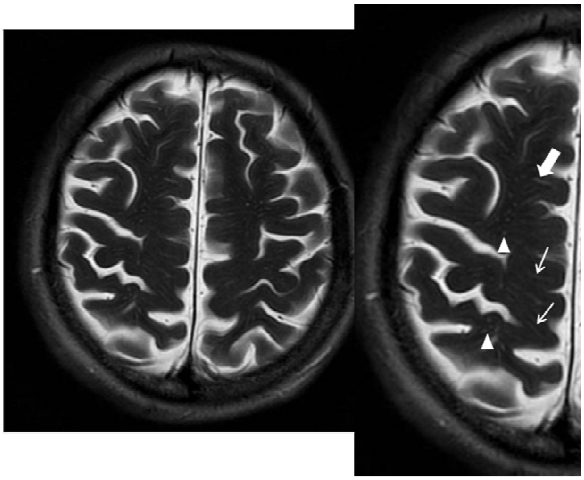
B. Magnified view showing EPVS at the level of the anterior perforated substance, where the anterior commissure is also seen (block arrow, pointing to left anterior commissure)



b. Centrum semiovale EPVS

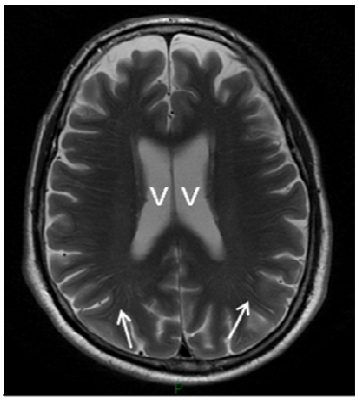
EPVS are seen in the centrum semiovale along the paths of the perforating medullary arteries as they enter the cortical gray matter over the high convexities and extend into the white matter. On standard axial T2MR imaging, EPVS in the centrum semiovale may have 3 different appearances depending on location scan orientation and perforator vessel orientation (Fig 7).

Figure 7. Varied configuration of EPVS in the centrum semiovale close to the vertex, with a combination of rounded (arrowheads), short linear (block arrow) and long linear (arrows) configurations



More inferiorly in the centrum semiovale, EPVS are frequently seen as linear, rather than rounded structures (Fig 8). Some scales separate EPVS in the centrum semiovale into round/oval and linear (Rouhl, 2008); in this scale, only 1 rating is given to EPVS in the centrum semiovale.

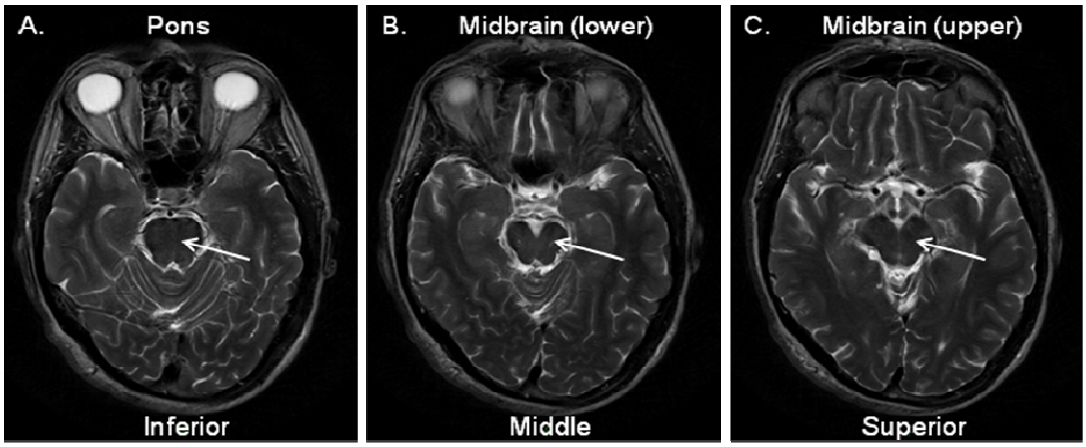
Figure 8. EPVS (arrows) visualised as linear structures in the centrum semiovale at the level of the bodies of the lateral ventricles (V)

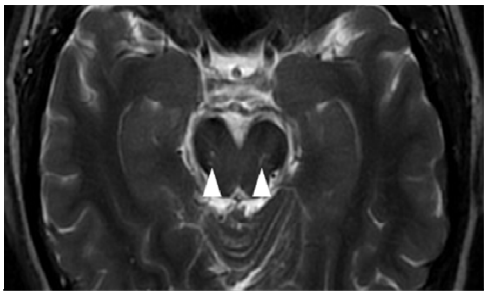


c. Midbrain EPVS

At the junction of the midbrain and pons (Fig 9), EPVS may be seen in relation to perforating arteries arising from the short paramedian (perforating) branches of the basilar artery. On standard axial T2MR imaging, EPVS in the midbrain normally appear as rounded foci of high signal. Normally, at least 2 slices should be reviewed when assessing midbrain EPVS.

Figure 9. A. Level of pons. B. Midbrain (at pons-midbrain junction), the third major site at which EPVS are seen. C. Slice above pons. A magnified view of the midbrain is also shown, demonstrating lower midbrain EPVS (arrowheads)





Section 3. Potential difficulties in EPVS rating

A. Variations in EPVS visibility

With current MRI scanners, some EPVS may be seen as faint, indistinct high signal structures in the basal ganglia, centrum semiovale and midbrain rather than clear, very high – near-CSF signal – structures (Fig 10, 11). A general impression of the region being rated should be used to choose a category, using the 'whole picture' and matching as closely as possible with the categories provided.

Figure 10. Multiple tiny EPVS visualised in the centrum semiovale, in a patient with additional movement artefact.

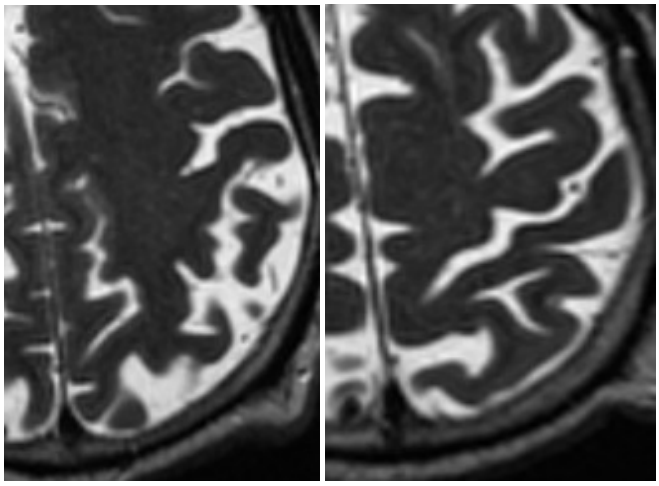
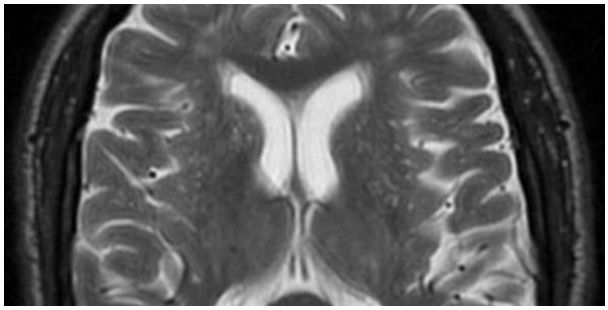


Figure 11. Multiple tiny basal ganglia EPVS, alongside several well visualised EPVS.



B. Background WMH

Where there are extensive WMHs, EPVS may be difficult to rate. In such cases, an estimate must be made of the closest rating category, using the appearance of non-involved white matter (where visible), and cortical gray matter. Review of all slices, including those at the vertex may be useful, where uninvolved white matter, and cortical gray matter, may be more easily visible (Fig 12). Some EPVS may also remain visible despite the presence of extensive WMH. Where WMH are non-confluent, rating may be more straightforward (Fig 13); in such cases, non-affected parenchyma should be used, and review of gray matter may also help.

Figure 12. Extensive deep WMH in the centrum semiovale, extending to the vertex. Appearances closer to the vertex (magnified image, bottom right image) suggest only mild EPVS

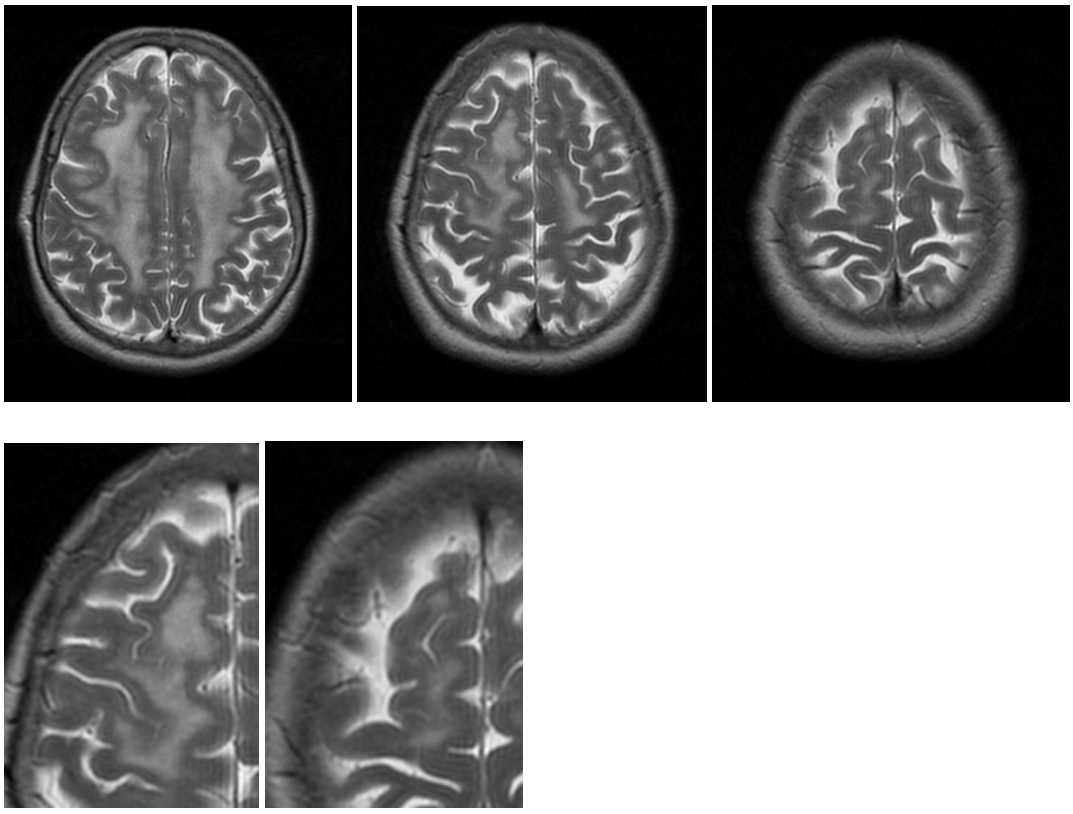
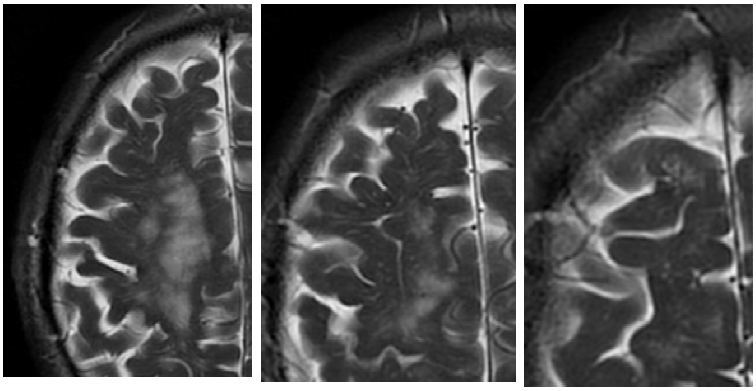


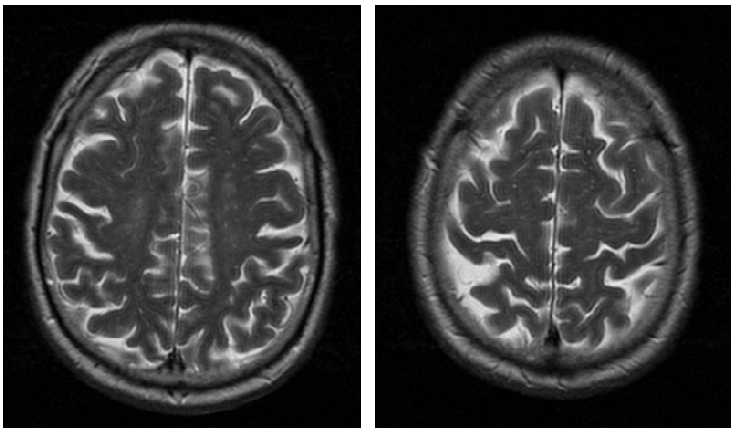
Figure 13. Non-confluent WMHs



C. Varying number of EPVS on different slices

The number of EPVS may vary depending on the slice selected. For example, in some patients, fewer EPVS will be visualised in the centrum semiovale at the level of the vertex compared to slices below this (Fig 14). After reviewing all relevant slices for the anatomical area being assessed, the highest number of EPVS should be recorded.

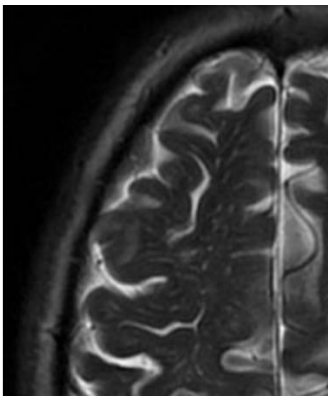
Figure 14. Axial T2-weighted images slices demonstrating varying numbers of EPVS at different levels of centrum semiovale, with fewer EPVS visible closer to the vertex (right image)



D. 'Double counting' of linear EPVS

Care should be taken to try to avoid counting linear EPVS twice, particularly in the centrum semiovale (Fig 15). Review of slices closer to the vertex – where EPVS are more often punctuate, rather than linear – may help in form an initial impression of the closest rating category. In all areas, review of adjacent slices can help reduce this potential problem.

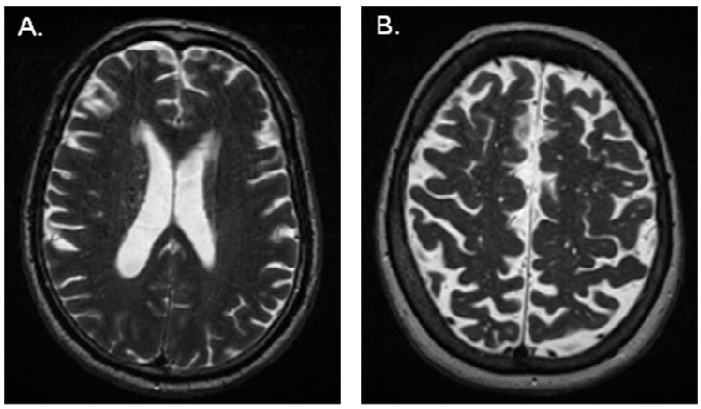
Figure 15. Illustration of potential pitfall of double-counting EPVS in the centrum semiovale



E. Poor scan quality, including movement

In some cases, EPVS rating may be made more difficult due to limited scan quality, particularly in patients with mild/moderate EPVS (Fig 16A) rather than frequent/ severe EPVS (Fig 16B). In such cases, an estimate of the closing rating category should be made.

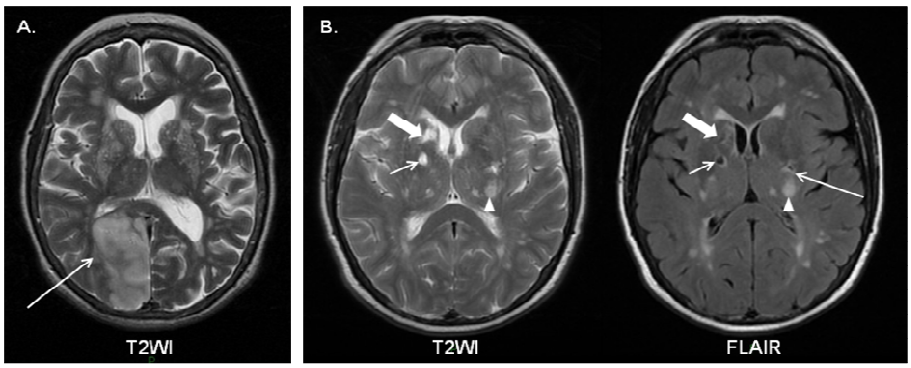
Figure 16. Limited MRI scan quality due to movement, making assessment of small structures more difficult, particularly where EPVS are mild (A) rather than frequent (B)



F. Asymmetry in background brain appearances

When background brain parenchyma is asymmetric due to the presence of another lesion, e.g. infarction (Fig 17A), EPVS should be rated on the other side where possible, or an estimate made of the closest category. Lacunes (fully, partially or non-cavitated) in the basal ganglia may also lead to difficulties in rating (Fig 17B); again, an estimate must be made of the closest category.

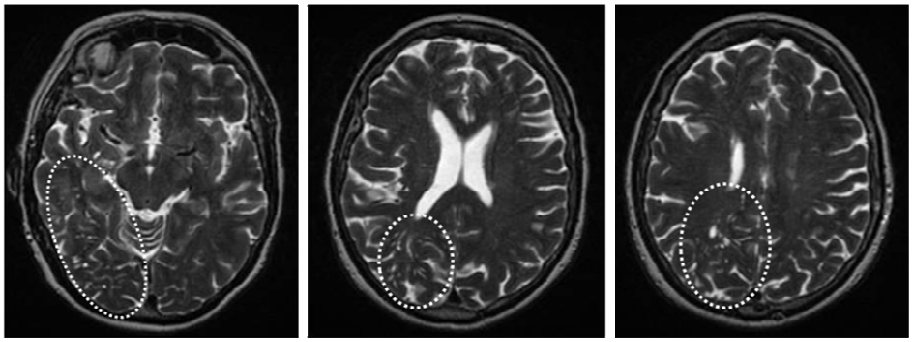
Figure 17. A. Asymmetry of background brain parenchyma due to an infarct in the right parieto-occipital lobe on T2-weighted MRI (arrow). B. Fully cavitated (short arrow), partially cavitated (thick arrow) and probably non-cavitated (arrowhead) lacunar lesions in the basal ganglia on T2 and FLAIR MRI. The exact nature of the lesion indicated by the long arrow is less certain - this could represent a cavitated lacune or EPVS with surrounding WMH



G. Asymmetry in EPVS

In some patients, EPVS may show significant asymmetry (Fig 18). In such cases, the side with the higher number should be counted

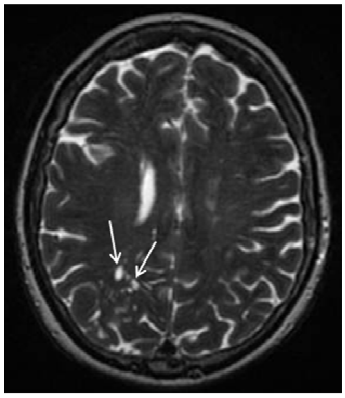
Figure 18. Marked asymmetry in EPVS, with a higher number of EPVS in the posterior cerebral artery territory on the right side (arrows)



H. Focally dilated EPVS

In some patients, focally dilated EPVS will be seen amongst uniformly dilated EPVS (Fig 19). The rating scale does not specifically take account of these.

Figure 19. Focally dilated EPVS (arrows) amongst uniformly dilated EPVS



I. Differentiating between the most severe categories of centrum semiovale EPVS

In many patient cohorts, the number of patients exhibiting the highest numbers/most severe degrees of EPVS in the centrum semiovale will be limited. Experience in rating the highest degrees of EPVS will thus be limited for the majority of people performing EPVS rating.

J. Variations in lesion load between cohorts

Rating of EPVS may vary with lesion load, as found in observer reliability testing for WMH,[9] therefore intermittent review of the full range of EPVS which may be encountered in patients – as demonstrated in this guide – is advised in order to help raters 'recalibrate'. Differences in MRI parameters may also contribute to observer differences, although this is a parameter which may be difficult to alter in the majority of cases.

Section 4. The EPVS scale

A. Rating categories & descriptions for each anatomical area

	Rating	Number of EPVS	Description
Basal ganglia and centrum semiovale	0	No EPVS	None
	1	1-10 EPVS	Mild
	2	11-20 EPVS	Moderate
	3	21-40 EPVS	Frequent
	4	>40 EPVS	Severe
Midbrain	0	No EPVS visible	Not present
	1	EPVS visible	Present

Notes:

Review both sides of the brain for EPVS, but use the *highest number from 1 side only*

Review all relevant slices, but use the slice with the highest number of EPVS

In cases where rating is difficult (e.g. due to movement, extensive WMH or uncertainty due to variations in EPVS visibility), select the closest category

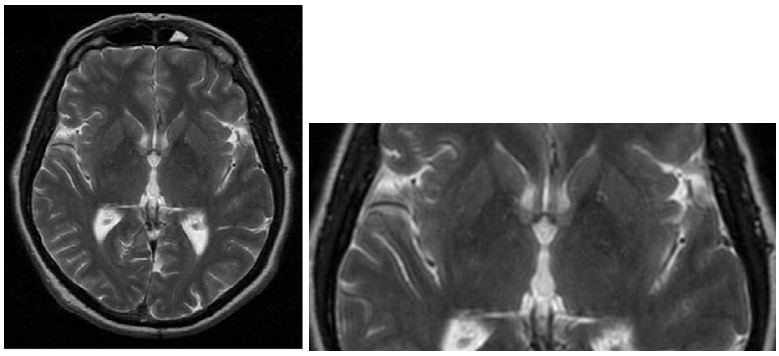
In cases of marked asymmetry (rare), record the score for the side of the brain with more EPVS

For basal ganglia EPVS, do not include EPVS in the anterior perforated substance

Imaging examples for rating categories

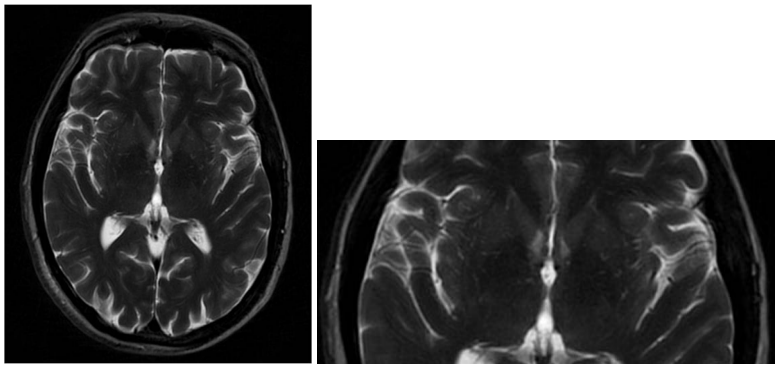
a. Basal ganglia

1-10 EPVS – category 1 (one example)

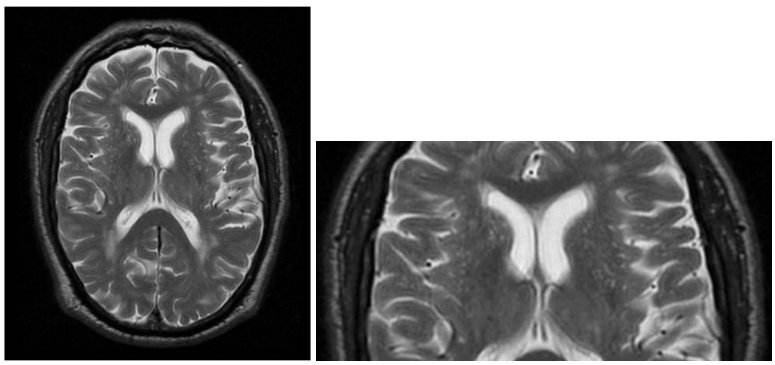


11-20 EPVS – category 2

Example 1 of 2



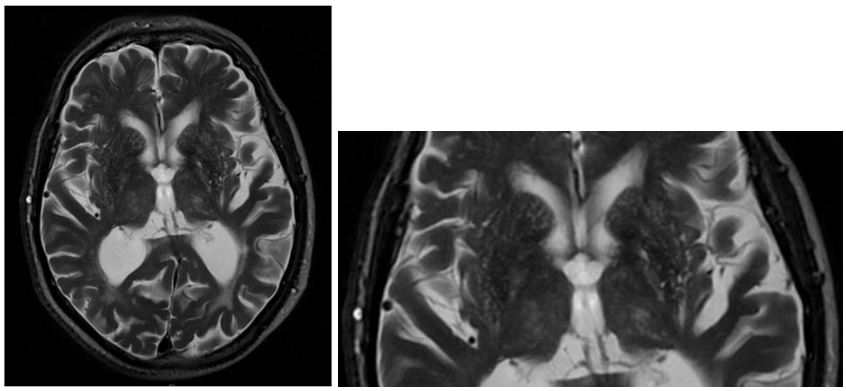
Example 2 of 2



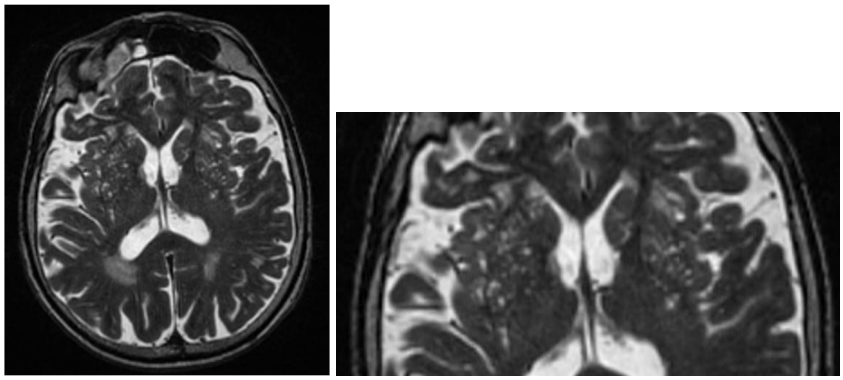
Basal ganglia

20-40 EPVS – category 3

Example 1 of 2

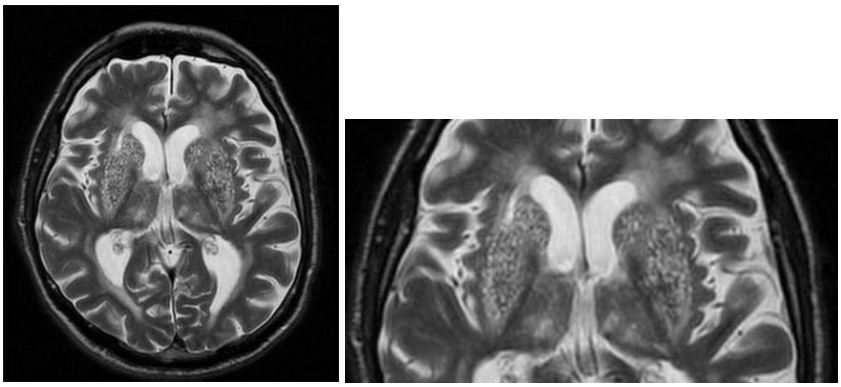


Example 2 of 2

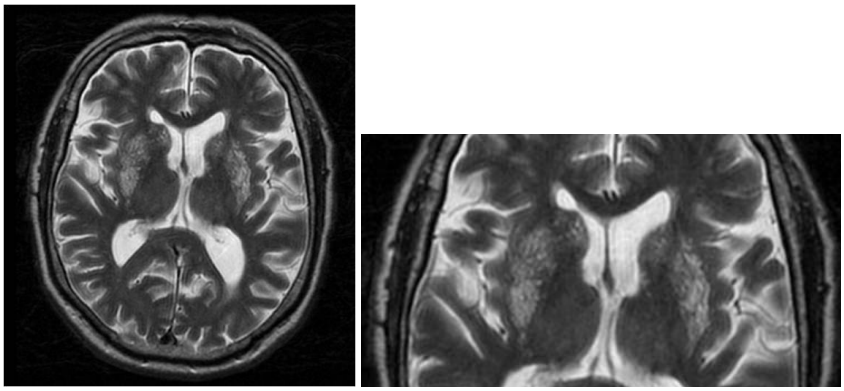


>40 EPVS – category 4

Example 1 of 2

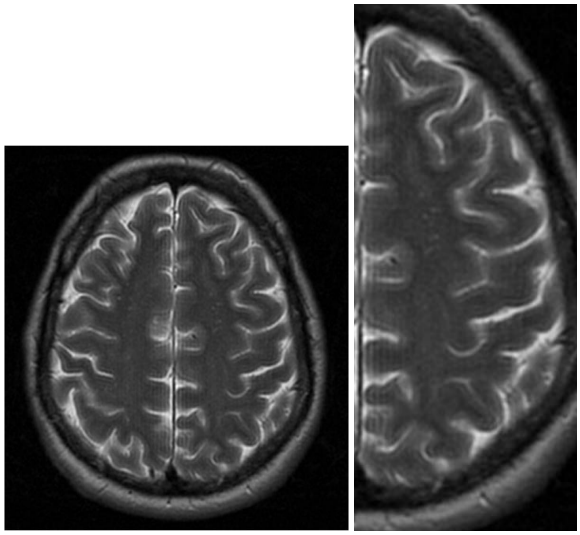


Example 2 of 2



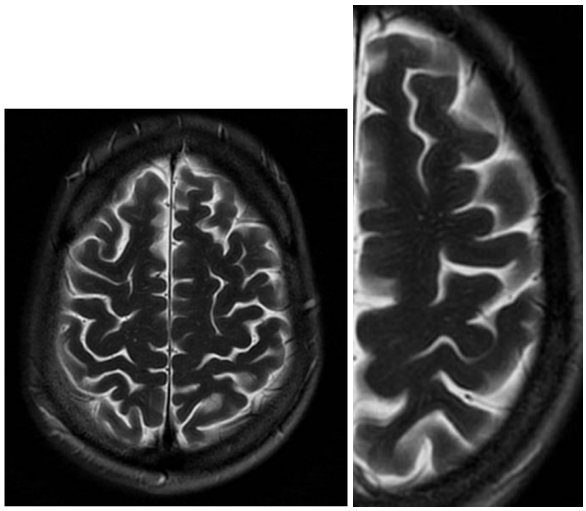
b. Centrum semiovale

1-10 EPVS – category 1



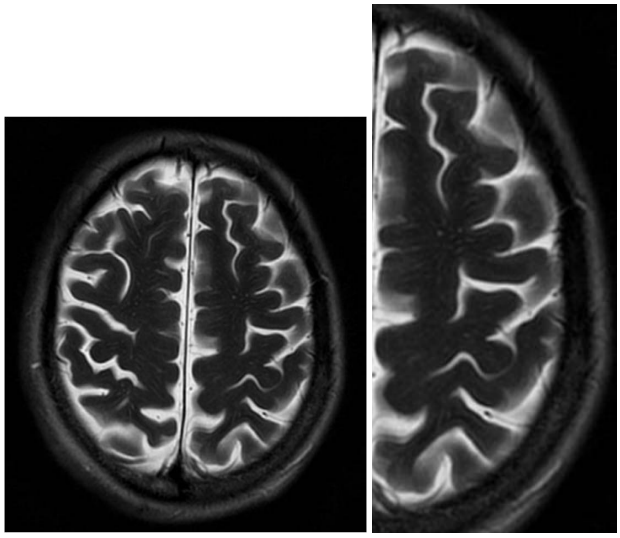
11-20 EPVS – category 2

Example 1 of 2

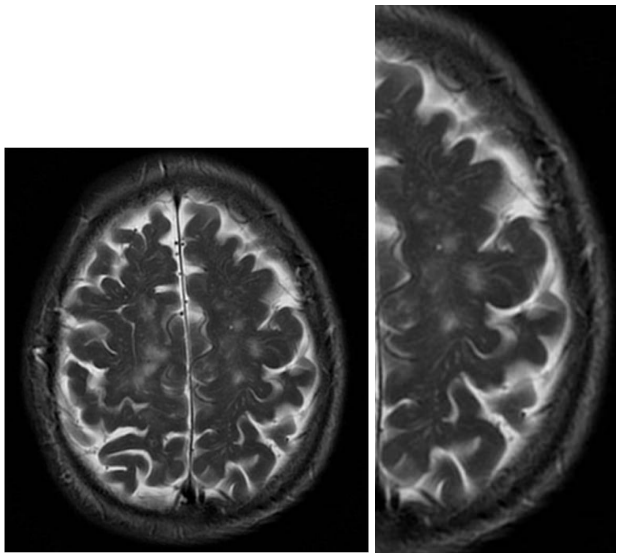


11-20 EPVS – category 2

Example 2 of 2

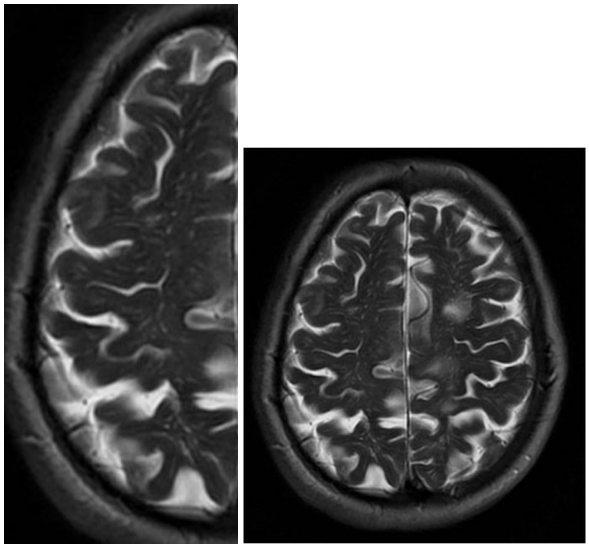


20-40 EPVS – category 3

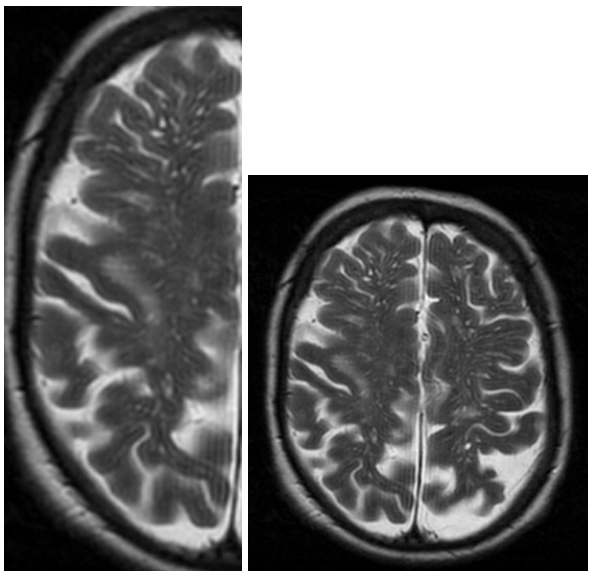


>40 EPVS – category 4

Example 1 of 2

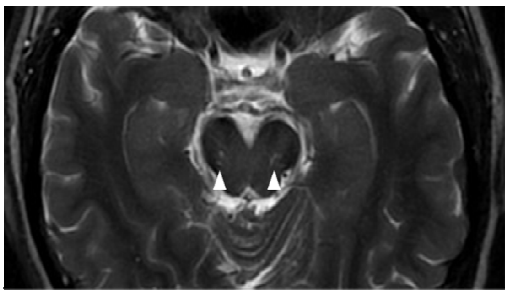


Example 2 of 2



c. Midbrain

EPVS visible – category 1



Conclusion

Because the clinical implications of EPVS remain to be established, there is still an opportunity to improve the reliability of EPVS assessment by the use of the EPVS rating scale, so that adequately powered, well designed studies will be able to answer the outstanding clinical concerns about their diagnostic and prognostic value within the spectrum of cerebral small vessel disease, and whether EPVS should influence patient management. Although we have developed and tested a visual rating scale, automated EPVS measurement methods may be possible with improved image processing algorithms in future.

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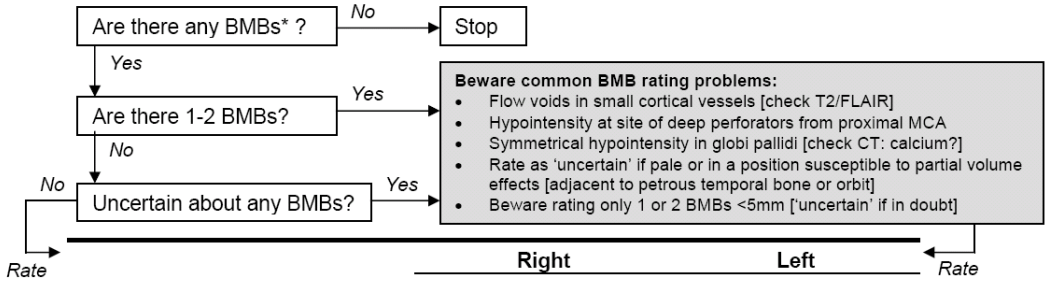
9. Wardlaw JM, Ferguson KJ, Graham C. White matter hyperintensities and rating scales – observer reliability varies with lesion load. *J Neurol* 2004;251:584-590.

Appendix 10. The Brain Observer MicroBleed Scale

Available at: http://www.sbirc.ed.ac.uk/documents/bombs-2008.pdf

Brain Observer Micro Bleed Scale (BOMBS)

Date of MRI ___ / ___ / ___ Date of birth ___ / ___ / ___ Study ID_____



	Right		Left	
	Certain	*Uncertain*	*Certain*	*Uncertain*
► **Cortex / grey-white junction**[1]				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Subcortical white matter**[2]				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Basal ganglia grey matter**[3]				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Internal and external capsule**				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Thalamus**				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Brainstem**				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Cerebellum**				
Number of BMBs <5mm				
Number of BMBs 5-10mm				

* Small, homogeneous, round foci of low signal intensity on T2*-weighted images of less than 10 mm in diameter. Low signal on T2* within infarcts or haemorrhagic strokes are not counted as BMBs.
[1] Includes subcortical BMBs that touch the grey-white matter junction.
[2] Includes periventricular white matter and deep portions of the centrum semiovale

Appendix 11. The Brain Observer MicroBleed Scale user guide

Available at: http://www.sbirc.ed.ac.uk/documents/bombs-userguide.pdf

A rating scale for brain microbleeds

The Brain Observer MicroBleed Scale [BOMBS][1] is a classification system devised to improve levels of interrater agreement about the presence, number, size and location of brain microbleeds (BMB). The use of a standard rating scale will hopefully minimise interobserver variation, enable cross-comparison between research groups and facilitate meta-analysis of BMB studies.

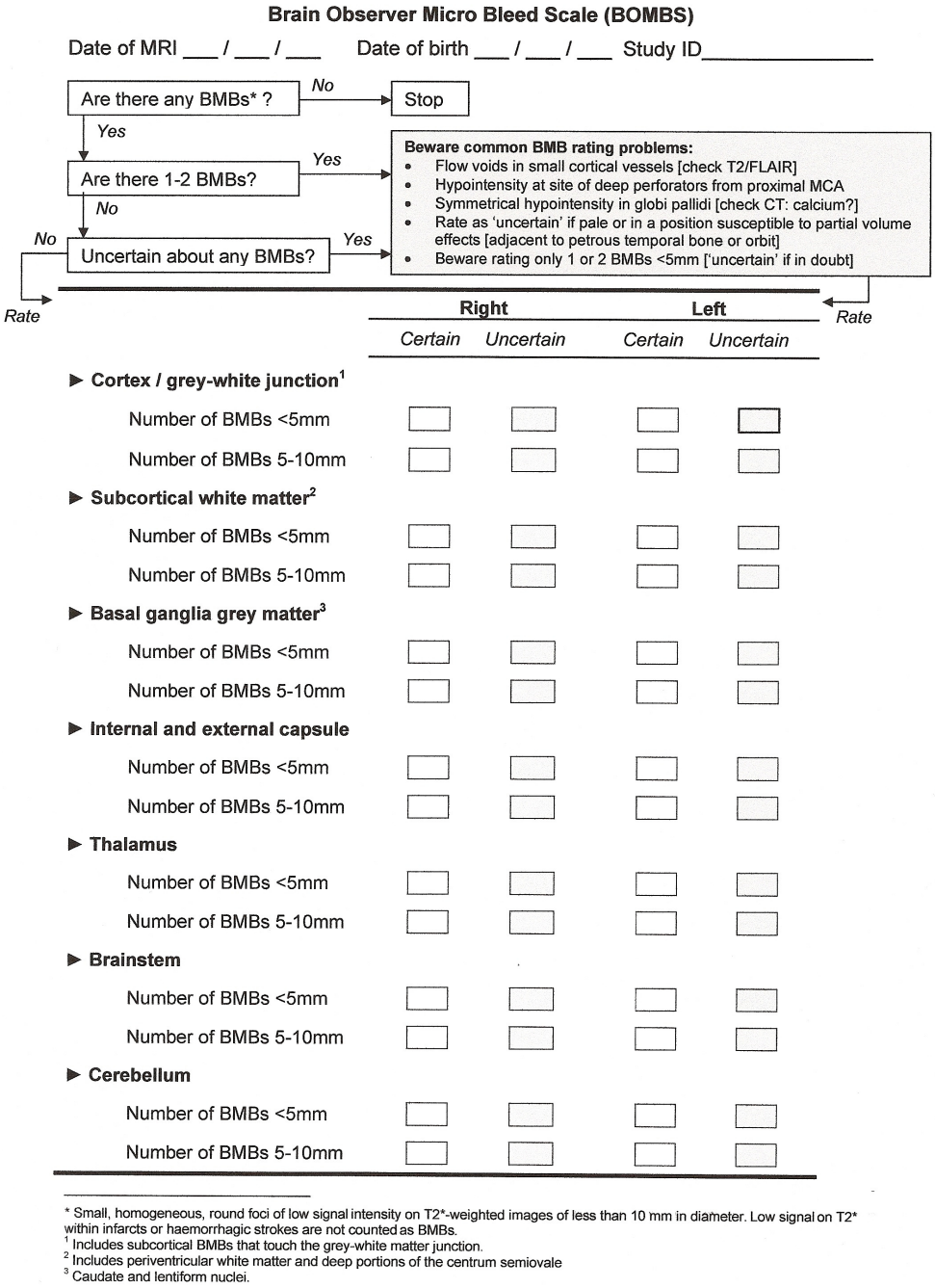
The BOMBS scale was developed after testing of an initial pilot scale by two observers highlighted several common difficulties in rating BMB, leading to interobserver variation. Ways of minimizing these difficulties were then incorporated into a revised scale – BOMBS – which improved interrater agreement.

Brain microbleeds are most easily identified on haem-sensitive MRI sequences, also known as T2* or gradient echo (GRE). However, BMB may also be visible on T2-weighted images, especially if they are numerous. T2-weighted images are particularly useful for demonstrating flow voids in cortical vessels, which can mimic BMB (see later). If there are no BMB evident on the GRE images, it is unlikely that they will be identified on other *routine* sequences, although all images should be reviewed as standard practice.

The BOMBS rating scale is shown on the next page. This is followed by a more detailed description of the main sections, including a diagram of the 7 anatomical locations which must be viewed for each scan. Finally, there are examples of ‘certain’ and ‘uncertain’ BMB and examples of common BMB mimics.

1 Cordonnier C, Potter GM, Jackson CA, Doubal F, Keir S, Sudlow CLM, Wardlaw JM, Al-Shahi Salman R. Improving interrater agreement about brain microbleeds: development of the Brain Observer MicroBleed Scale (BOMBS). *Stroke* 2009;40:94-99.

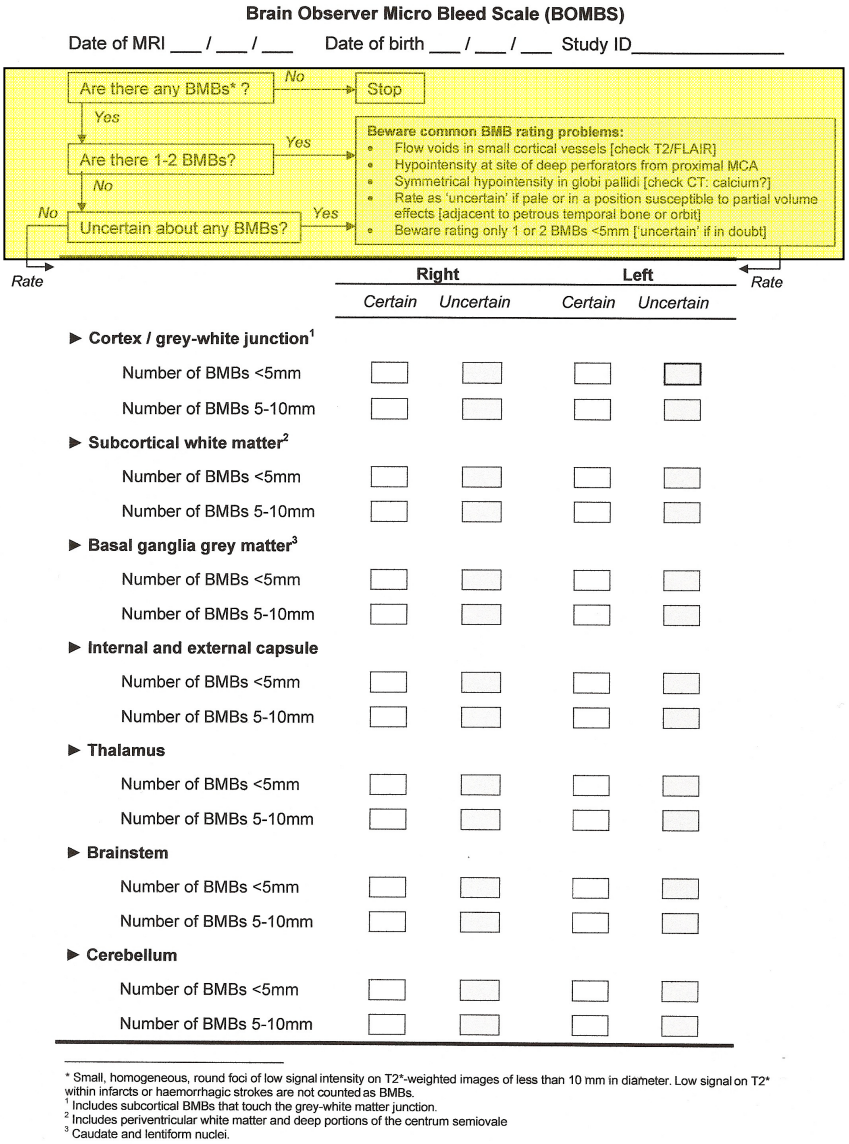
The Brain Observer MicroBleed Scale (BOMBS)



* Small, homogeneous, round foci of low signal intensity on T2*-weighted images of less than 10 mm in diameter. Low signal on T2* within infarcts or haemorrhagic strokes are not counted as BMBs.
[1] Includes subcortical BMBs that touch the grey-white matter junction.
[2] Includes periventricular white matter and deep portions of the centrum semiovale
[3] Caudate and lentiform nuclei.

Description of BOMBS

The top section of the scale (yellow) consists of a flow chart, highlighting the two main situations in which common problems should be reviewed: 1. If there are only a few BMB, then particular care should be taken over mimics, and 2. If the lesion is in a location where 'BMB mimics' are common - basal ganglia (at site of deep MCA perforators), cortex and adjacent to petrous apex / orbit (see examples below).



* Small, homogeneous, round foci of low signal intensity on T2*-weighted images of less than 10 mm in diameter. Low signal on T2* within infarcts or haemorrhagic strokes are not counted as BMBs.
[1] Includes subcortical BMBs that touch the grey-white matter junction.
[2] Includes periventricular white matter and deep portions of the centrum semiovale
[3] Caudate and lentiform nuclei.

There are 7 locations which must be assessed on both sides of the brain. Descriptions of 3 of these (yellow) are given at the bottom of the scale as shown. The diagram on the next page demonstrates these locations.

Brain Observer Micro Bleed Scale (BOMBS)

Date of MRI ___ / ___ / ___ Date of birth ___ / ___ / ___ Study ID_____

Are there any BMBs* ? — No → Stop

Yes ↓

Are there 1-2 BMBs? — Yes → **Beware common BMB rating problems:**
- Flow voids in small cortical vessels [check T2/FLAIR]
- Hypointensity at site of deep perforators from proximal MCA
- Symmetrical hypointensity in globi pallidi [check CT: calcium?]
- Rate as 'uncertain' if pale or in a position susceptible to partial volume effects [adjacent to petrous temporal bone or orbit]
- Beware rating only 1 or 2 BMBs <5mm ['uncertain' if in doubt]

No ↓

Uncertain about any BMBs? — Yes → (Beware rating only 1 or 2 BMBs <5mm ['uncertain' if in doubt])

No → Rate

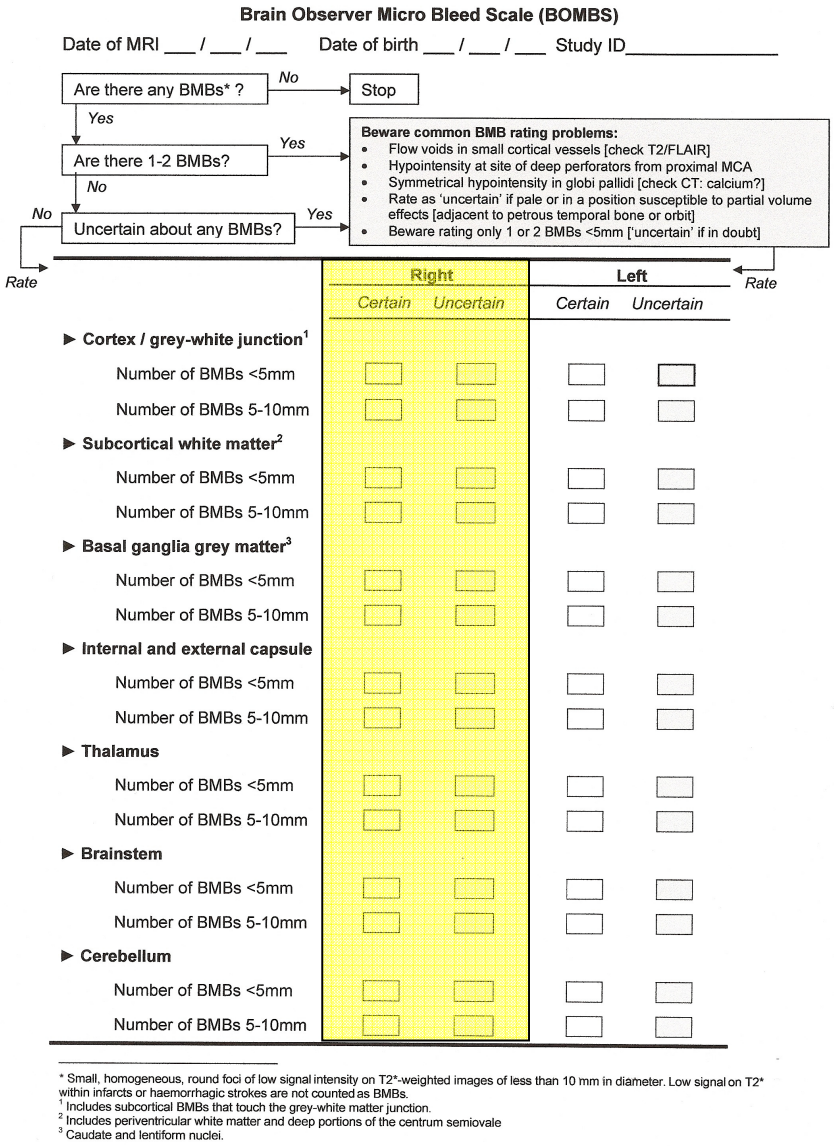
	Right		Left		
	Certain	*Uncertain*	*Certain*	*Uncertain*	
▶ **Cortex / grey-white junction**[1]					Rate
Number of BMBs <5mm	☐	☐	☐	☐	
Number of BMBs 5-10mm	☐	☐	☐	☐	
▶ **Subcortical white matter**[2]					
Number of BMBs <5mm	☐	☐	☐	☐	
Number of BMBs 5-10mm	☐	☐	☐	☐	
▶ **Basal ganglia grey matter**[3]					
Number of BMBs <5mm	☐	☐	☐	☐	
Number of BMBs 5-10mm	☐	☐	☐	☐	
▶ **Internal and external capsule**					
Number of BMBs <5mm	☐	☐	☐	☐	
Number of BMBs 5-10mm	☐	☐	☐	☐	
▶ **Thalamus**					
Number of BMBs <5mm	☐	☐	☐	☐	
Number of BMBs 5-10mm	☐	☐	☐	☐	
▶ **Brainstem**					
Number of BMBs <5mm	☐	☐	☐	☐	
Number of BMBs 5-10mm	☐	☐	☐	☐	
▶ **Cerebellum**					
Number of BMBs <5mm	☐	☐	☐	☐	
Number of BMBs 5-10mm	☐	☐	☐	☐	

* Small, homogeneous, round foci of low signal intensity on T2*-weighted images of less than 10 mm in diameter. Low signal on T2* within infarcts or haemorrhagic strokes are not counted as BMBs.
[1] Includes subcortical BMBs that touch the grey-white matter junction.
[2] Includes periventricular white matter and deep portions of the centrum semiovale
[3] Caudate and lentiform nuclei.

Locations to be assessed in BOMBS (excluding cerebellum and brainstem)

See Figure 15.

Finally, BMB should be rated as 'certain' and 'uncertain' for each side of the brain, in the appropriate row for rating size (<5mm, 5-10mm). Examples of BMB and their common mimics are shown on the following 5 pages.



BMB examples

Below are MR images which have been chosen to demonstrate examples of ‘certain’ and ‘uncertain’ microbleeds.

‘Certain’ BMB

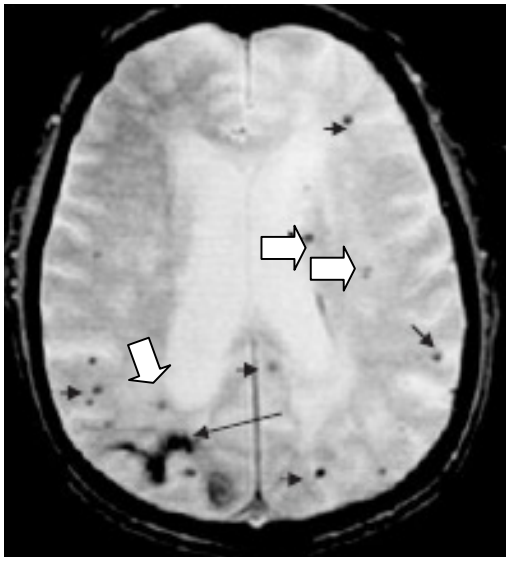
Locations with BMB: Cortex/grey-white matter junction (both sides)

Internal capsule/external capsule (white arrow)

Thalamus (black arrows)

Note: The BMB in the right thalamus (thick black arrow) measures 5-10mm

'Certain' BMB

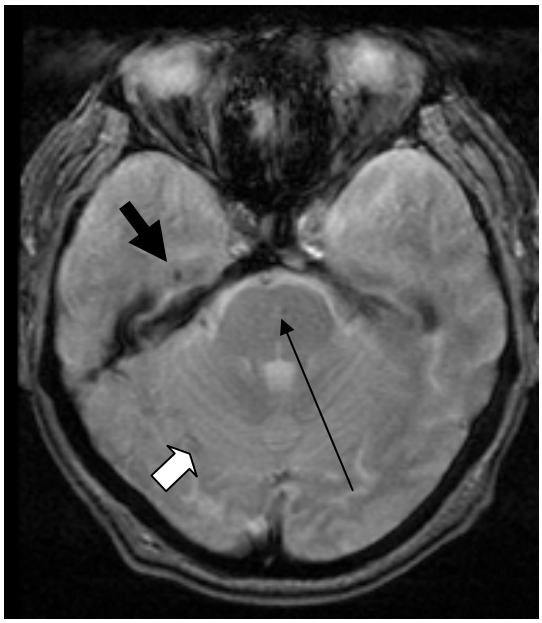


Locations: Cortex/grey-white matter junction (both sides; not all labelled)

Deep white matter (white arrows)

Note: All BMB measure <5mm – however, there is also an old right parietal haemorrhage (long arrow)

'Certain' BMB



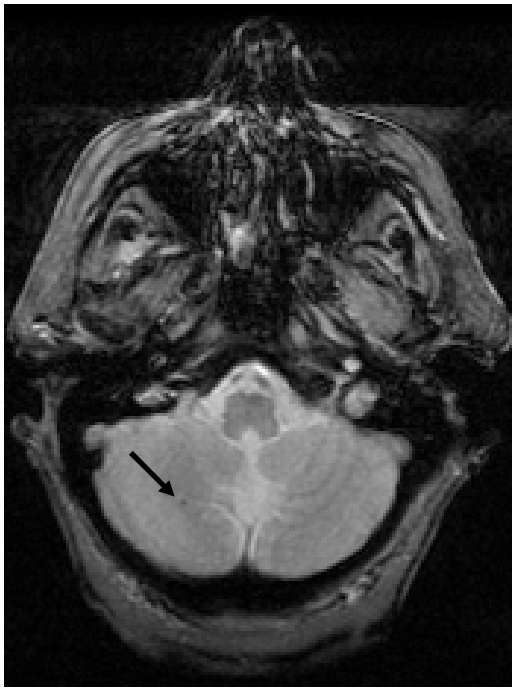
GRE

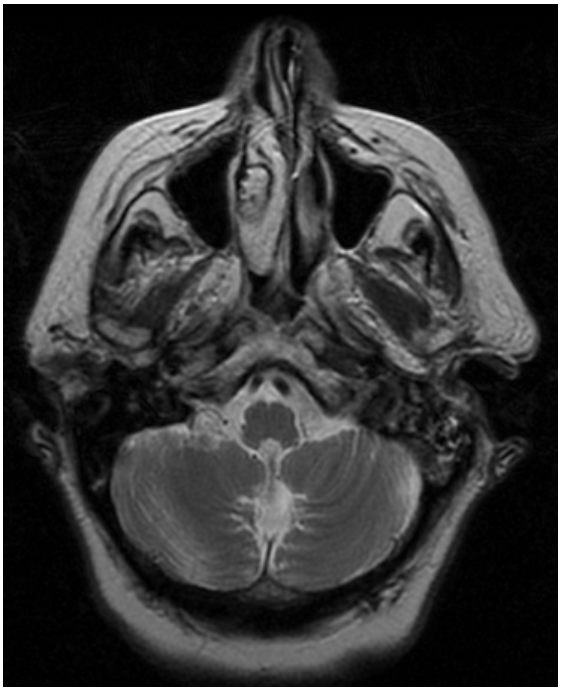
T2

Location: Left upper pons (long arrow)

Note: There are also BMB mimics on this scan - from partial volume artifact (short black arrow) and small cortical vessels (white arrow)

'Certain' BMB



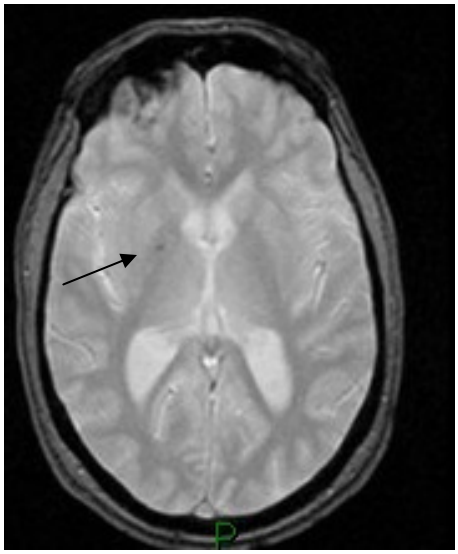


GRE **T2**

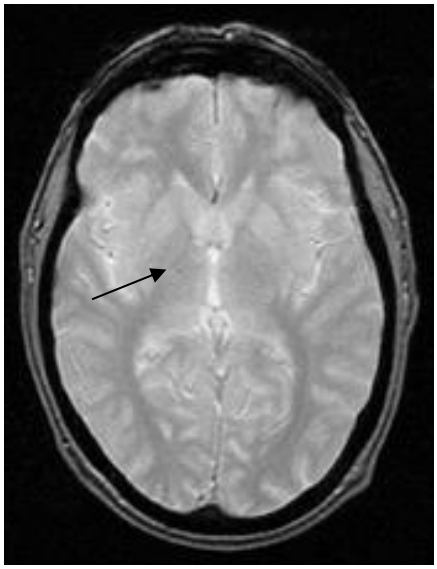
Location: Right cerebellum (arrow)

Note: There is no visible flow void on the corresponding T2-weighted image

‘Uncertain’ BMB



Here, there is a pale unilateral low signal lesion in the right internal capsule. In this case, no CT was available to check for asymmetric calcification. This lesion would be rated as ‘uncertain’.

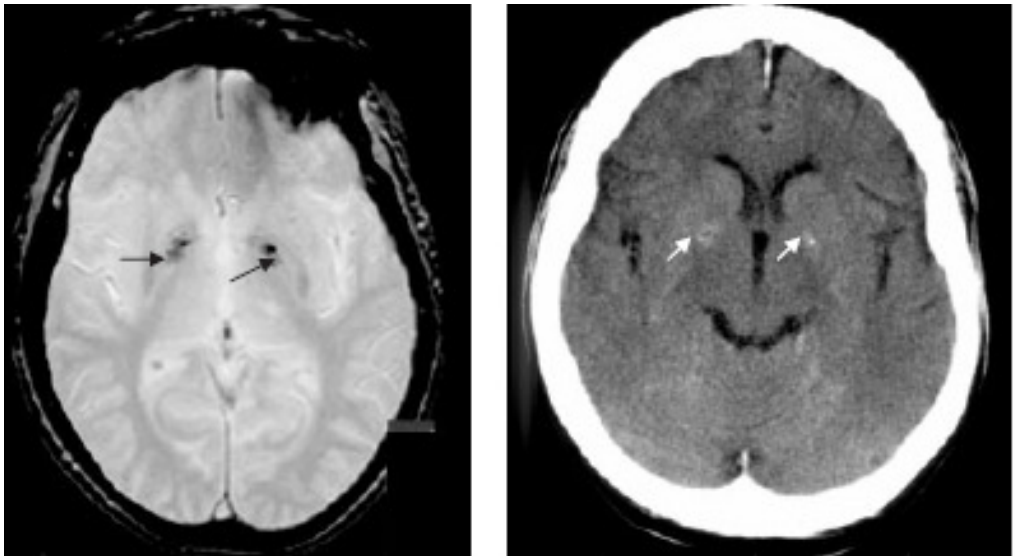


Here, the lesion is smaller and even paler than in the previous case and would therefore be rated as ‘uncertain’.

Remember that when there are 1-2 BMB, rating may be more difficult.

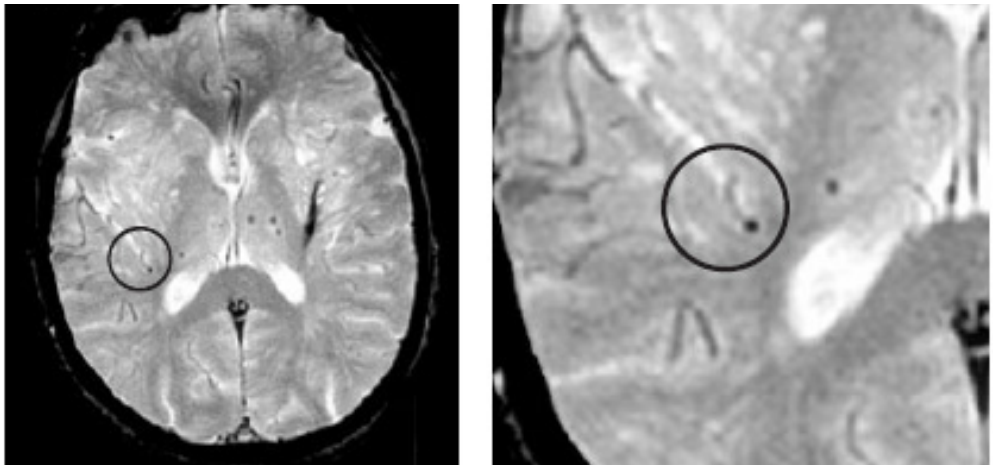
Examples of common ‘BMB mimics’

1. Basal ganglia calcification



In this case, axial non-contrast CT (right) confirms the presence of bilateral basal calcification, mimicking BMB on gradient echo MRI (left)

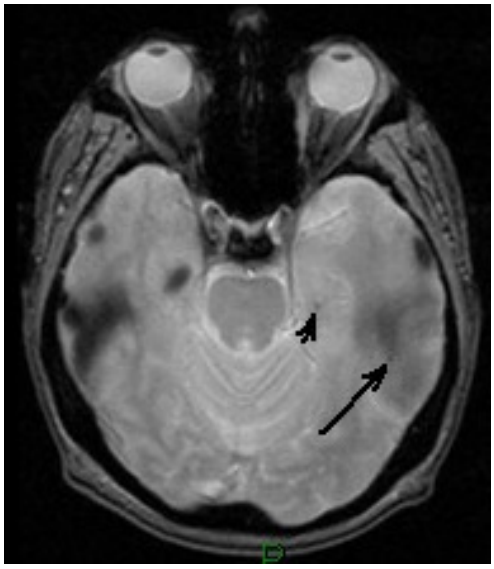
2. Cortical vessels



In this case, the circled ‘BMB’ (magnified image on right) is due to a sulcal vessel seen in cross section - with a visible vessel leading up to it.

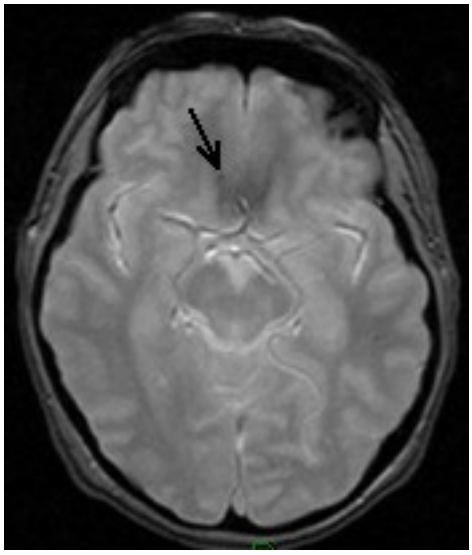
3. Partial volume artefact

A. From petrous temporal bone



Note the small apparent ‘pale’ BMB in the left temporal lobe (arrows) – these are due to partial volume from the petrous temporal bone and therefore not BMB.

B. From orbit



Similarly, this ‘pale BMB’ in the right medial frontal lobe (arrow) is due to partial volume artifact from the orbit, which lies immediately inferior to this slice.

Conclusions

Because the clinical implications of BMB remain to be established, there is still an opportunity to improve the reliability of BMB assessment by the use (and further development) of the BOMBS rating scale, so that adequately powered, well designed studies will be able to answer the outstanding clinical concerns about their diagnostic and prognostic value, and whether presence of BMB should influence the prescription of antiplatelet, anticoagulant, or thrombolytic drugs.

Appendix 12. Publications

Improving Interrater Agreement About Brain Microbleeds
Development of the Brain Observer MicroBleed Scale (BOMBS)

Charlotte Cordonnier, PhD; Gillian M. Potter, FRCR; Caroline A. Jackson, MSc; Fergus Doubal, MRCP; Sarah Keir, MD; Cathie L.M. Sudlow, DPhil; Joanna M. Wardlaw, FMedSci; Rustam Al-Shahi Salman, PhD

Background and Purpose—If the diagnostic and prognostic significance of brain microbleeds (BMBs) are to be investigated and used for these purposes in clinical practice, observer variation in BMB assessment must be minimized.

Methods—Two doctors used a pilot rating scale to describe the number and distribution of BMBs (round, low-signal lesions, <10 mm diameter on gradient echo MRI) among 264 adults with stroke or TIA. They were blinded to clinical data and their counterpart's ratings. Disagreements were adjudicated by a third observer, who informed the development of a new Brain Observer MicroBleed Scale (BOMBS), which was tested in a separate cohort of 156 adults with stroke.

Results—In the pilot study, agreement about the presence of ≥1 BMB in any location was moderate (κ=0.44; 95% CI, 0.32–0.56), but agreement was worse in lobar locations (κ=0.44; 95% CI, 0.30–0.58) than in deep (κ=0.62; 95% CI, 0.48–0.76) or posterior fossa locations (κ=0.66; 95% CI, 0.47–0.84). Using BOMBS, agreement about the presence of ≥1 BMB improved in any location (κ=0.68; 95% CI, 0.49–0.86) and in lobar locations (κ=0.78; 95% CI, 0.60–0.97).

Conclusion—Interrater reliability concerning the presence of BMBs was moderate to good, and could be improved with the use of the BOMBS rating scale, which takes into account the main sources of interrater disagreement identified by our pilot scale. **(*Stroke*. 2009;40:94-99.)**

Key Words: brain microbleed ■ rating scale ■ interrater reliability ■ classification ■ stroke

In stroke medicine, the burning questions about brain microbleeds (BMBs) concern their diagnostic significance (for example, for the ante mortem diagnosis of cerebral amyloid angiopathy and other disorders) and whether BMBs should influence the use of antithrombotic and thrombolytic drugs.[1] If the diagnostic and prognostic significances of BMBs are to be investigated and used for these purposes in clinical practice, then definitive research studies should fulfill a variety of prerequisites,[2] including knowledge of the usefulness of the scales used to rate BMBs as well as the intrarater and interrater variation of the individual researchers using the scales.

Previous studies have reported variable levels of interrater agreement among 2 or 3 observers (Table 1).[3–15] Studies of interrater reliability found kappa values ranging from 0.33 (fair)[3] to 0.88 (excellent);[10,11] however, most found κ>0.7, but sample sizes were small, 95% CIs were not always provided, and the properties of the rating scales used were not described.

In view of the variation in reported interrater agreement, the potential for a rating scale to improve levels of agreement, and the absence of a rating scale for BMBs, we further quantified interrater agreement about the presence, number, size, and location of BMBs to develop a simple BMB classification scheme that might minimize observer variation.

Subjects and Methods

Study Population

We studied a subset of patients from a hospital-based stroke register (the Edinburgh Stroke Study, http://www.dcn.ed.ac.uk/ess/)[16] (Table 2). Consecutive consenting stroke and transient ischemic attack (TIA) patients were recruited to the register from outpatient clinics and hospital admissions (total n=2160). In the current study we included those patients who had undergone at least 1 MRI scan with gradient echo (GRE) sequences (n=264). If a patient had >1 MRI, then we used the earliest scan.

MRI Protocols

MRIs were performed on a GE Signa LX 1.5-Tesla machine with 22-mT m^{-1} maximum strength gradients using the manufacturer-supplied quadrature birdcage head coil. Diagnostic MR imaging included (all axial sequences): diffusion-weighted (TR, 9999; TE, 98.8; matrix, 128×128; FoV, 24×24; slice thickness, 5 mm; slice gap, 1 mm; NEX, 1 [where TR indicates relaxation time; TE, echo time; FoV, field of view; NEX, number of excitations]); T2-weighted (TR, 6300; TE, 107; matrix, 256×256; FoV, 24×18; slice thickness,

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.108.526996**

Table 1. Published Studies of Interrater Agreement About BMBs

Study	N of Observers	N of MRI Scans	Type of Population	Prevalence of BMBs	Type of Analysis	Statistical Test Used	Interobserver Agreement (95% CI When Available)
Lee et al[13]	2	125	ICH	66%	Total N of BMBs	Spearman correlation	0.81
Greenberg et al[6]	2	32	Lobar ICH	Not specified	Total N of BMBs	Intraclass correlation	0.97
Viswanathan et al[12]	2	20	CADASIL	35%	Total N of BMBs	Intra-class correlation	0.96
Lee et al[11]	2	102	Stroke and HTN	65%	Grade of BMBs (4 grades)	Kappa	0.88 (0.81–0.95)
Jeon et al[10]	2	63	ICH	68%	Presence or absence of BMBs	Kappa	0.88
Lee et al[9]	2	143	ICH vs control	97% vs 56%	Not specified	Kappa	0.87
Lee et al[8]	2	26	ICH	Not specified	Not specified	Kappa	0.86
Kakuda et al[7]	2	70	Ischemic stroke treated with IV tPA	16%	Presence or absence of BMBs	Kappa	0.77 (0.55–0.99)
Greenberg et al[6]	2	15	Lobar ICH	Not specified	Presence or absence of new BMBs	Kappa	0.73
Lemmens et al[14]	2	342	TIA or ischemic stroke	26%	Presence or absence of BMBs	Kappa	0.71 (0.59–0.82)
Kwa et al[5]	2	221	Ischemic stroke and other vascular diseases	14%	Not specified	Kappa	0.6
Roob et al[4]	3	280	Healthy	6%	Presence or absence of BMBs	Kappa	0.40–0.65
Jeerakathil et al[3]	3	222	Healthy	5%	Presence or absence of BMBs	Kappa	0.33–0.57
Vernooij et al[15]	2	300	Healthy	24%	Presence or absence of BMBs	Kappa	0.85

Updated from Cordonnier et al Brain 2007.[2]

CADASIL indicates cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; HTN, arterial hypertension; ICH, intracerebral hemorrhage; IV, intravenous; TIA, transient ischemic attack; tPA, tissue plasminogen activator.

5 mm; slice gap, 1.5 mm; NEX, 2); fluid-attenuated inversion recovery (TR, 9002; TE, 147; matrix, 256×256; FoV, 24×24; slice thickness, 5 mm; slice gap, 1.5 mm; NEX, 1); and GRE (T2*; TR, 620; TE, 15; flip angle, 20; FoV, 24×18; matrix, 256×192; slice thickness, 5 mm; slice gap, 1 mm; NEX, 2).

Brain Microbleed Rating

A neuroradiologist (G.M.P.) and a neurologist (C.C.), both with experience in rating BMBs, independently assessed all MRI sequences on cut film, belonging to all 264 adults, using a pilot BMB rating scale, which required the reader to quantify BMBs subdivided by size (<5 mm, 5–10 mm), side of brain (left, right), and location (lobar [cortex/gray–white junction; subcortical white matter], deep [basal ganglia grey matter; internal and external capsules; thalamus], and posterior fossa [brain stem; cerebellum]; Figure 1). All BMBs were measured manually. Each observer was blinded to clinical data and to the other observer's ratings. BMBs were defined as homogeneous, round foci, <10 mm diameter (no minimum size was specified), of low signal intensity on GRE T2*-weighted MRI. The observers were aware of the main BMB mimics. Low-signal lesions on GRE T2* within a lesion compatible with an infarct were regarded as hemorrhagic transformations rather than BMBs.

Development and Testing of the Brain Observer MicroBleed Scale (BOMBS)

After the assessment of interrater agreement with the pilot scale, a senior neuroradiologist (J.M.W.) reviewed MRI scans about which the 2 observers disagreed in their BMB ratings. We developed the Brain Observer MicroBleed Scale (BOMBS) to account for some of the common sources of disagreement and other major problems encountered (see Supplemental Figure I, available online at http://stroke.ahajournals.org and www.sbirc.ed.ac.uk/imageanalysis.html). We re-evaluated agreement between the same 2 observers using BOMBS in a different set of patients undergoing identical MRI sequences and parameters to quantify BMBs subdivided by size, side of brain, and location (as before), but with the addition of a further subdivision into "certain" and "uncertain" BMB categories. The study population for the assessment of BOMBS was a series of 156 patients with stroke (different to the 264 in whom the pilot rating scale was tested) who had been recruited in 2 other stroke studies requiring MRI. Both studies recruited from the same hospital sources as the Edinburgh Stroke Study. One study recruited patients with lacunar or nondisabling cortical ischemic stroke (the Mild Stroke Study); the other included outpatients presenting >1 week after a mild stroke, in whom CT scanning would not discriminate between ischemic or hemorrhagic stroke, requiring MRI for stroke subtyping.

Statistical Analyses

We quantified observer agreement using the unweighted κ statistic for nominal data (such as dichotomized presence versus absence of ≥1 BMB) analyzed in any brain location and in separate brain areas (lobar, deep, and posterior fossa). When using BOMBS, we calculated κ for BMBs rated certain, and for BMBs rated certain or uncertain. Intraclass correlation coefficients were calculated to assess agreement between observers for the overall numbers of BMBs. When exploring interobserver reliability in measurements of BMB size, we restricted our analysis to MRI scans on which both raters had observed definite BMBs in the same brain location. All analyses were performed in SPSS version 13.0, except for confidence inter-

Table 2. Characteristics of the Study Populations and Interrater Agreement (simple [unweighted] kappa statistic) About the Presence of ≥1 BMB in Separate Brain Areas or in Any Brain Location Using the Pilot Rating Scale and Using BOMBS

	Pilot Population, n=264	BOMBS Population, n=156
Median age (IQR)	72 (60–78)	66 (56–75)
Ischaemic stroke	235 (90%)	151 (97%)
Intracerebral hemorrhage	10 (4%)	5 (3%)
TIA	15 (6%)	0
History of stroke or TIA	79 (30%)	22 (14%)
History of treated hypertension	135 (51%)	81 (52%)

	Pilot Rating Scale			BOMBS Rating Scale					
				Certain and Uncertain BMBs			Certain BMBs		
	Observer A	Observer B	Kappas 0 vs ≥1 BMB (95% CI)	Observer A	Observer B	Kappas 0 vs ≥1 BMB (95% CI)	Observer A	Observer B	Kappas 0 vs ≥1 BMB (95% CI)
All Locations									
Patients with ≥1 BMB; % (95% CI)	105; 40 (34–46)	54; 20 (16–26)	0.44 (0.32–0.56)	28; 18 (13–25)	39; 25 (19–32)	0.38 (0.19–0.57)	18; 12 (7–18)	21; 14 (9–20)	0.68 (0.49–0.86)
N of lesions on all scans	320	362		67	107		43	61	
Median N of lesions per patient (IQR)	1 (1–3)	2 (1–7.25)		2 (1–2)	1 (1–2.5)		1.5 (1–2)	2 (1–2.5)	
Lobar									
Patients with ≥1 BMB; % (95% CI)	71; 27 (22–33)	39; 15 (11–20)	0.44 (0.30–0.58)	16; 10 (6–16)	24; 15 (11–22)	0.49 (0.26–0.71)	12; 8 (5–13)	13; 8 (5–14)	0.78 (0.60–0.97)
N of lesions on all scans	188	231		29	48		19	28	
Median N of lesions per patient (IQR)	1 (1–2)	2 (1–6.5)		1 (1–2)	1 (1–2)		1 (1–2)	1 (1–2)	
Deep									
Patients with ≥1 BMB; % (95% CI)	50; 19 (15–24)	30; 11 (8–16)	0.62 (0.48–0.76)	17; 11 (7–17)	22; 14 (10–20)	0.39 (0.14–0.63)	9; 6 (3–11)	12; 8 (5–13)	0.54 (0.25–0.83)
N of lesions on all scans	95	88		28	43		18	19	
Median N of lesions per patient (IQR)	1 (1–2)	2 (1–4)		1 (1–1)	1 (1–2)		1 (1–1)	1 (1–1)	
Posterior fossa									
Patients with ≥1 BMB; % (95% CI)	23; 9 (6–13)	18; 7 (4–11)	0.66 (0.47–0.84)	5; 3 (1–7)	6; 4 (2–8)	0.91 (0.72–1.00)	3; 2 (1–6)	6; 4 (2–8)	0.66 (0.28–1.00)
No. of lesions on all scans	37	43		10	16		6	14	
Median N of lesions per patient (IQR)	1 (1–2)	2 (1–4)		1 (1–2)	1 (1–4)		1 (1–2.5)	1 (1–4)	

IQR indicates interquartile range; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; N, number.

vals for κ, which were calculated using Confidence Interval Analysis software.[17]

Ethics

Ethical approval was granted by the Lothian Research Ethics Committee.

Results

Study of Interrater Reliability Using a Pilot Rating Scale

Agreement about the presence/absence of ≥1 BMB in any location in the brain was moderate (κ, 0.44; 95% CI, 0.32–0.56), but it appeared to be better in deep and posterior fossa locations when compared to lobar areas (Table 2). The intraclass correlation coefficient for the overall number of BMBs was 0.91 (95% CI, 0.88–0.93). The 2 observers disagreed about the presence of ≥1 BMB on 65 MRI scans. When these disagreements were reviewed by a third observer (J.M.W.), most were found to occur when there was doubt about whether there was 1 BMB on a scan or none. The main causes for disagreement were common BMB mimics such as vascular flow voids (cortical and perforator vessels), irregularly shaped lesions, lesions too pale to be confident about them being a BMB, partial volume artifacts from the petrous temporal bone or orbit, and variable signal dropout (Figure 2).

Development and Testing of the BOMBS

We revised the pilot rating scale on the basis of the causes of the observed disagreements to develop the BOMBS (Supplemental Figure I). Interrater agreement about the

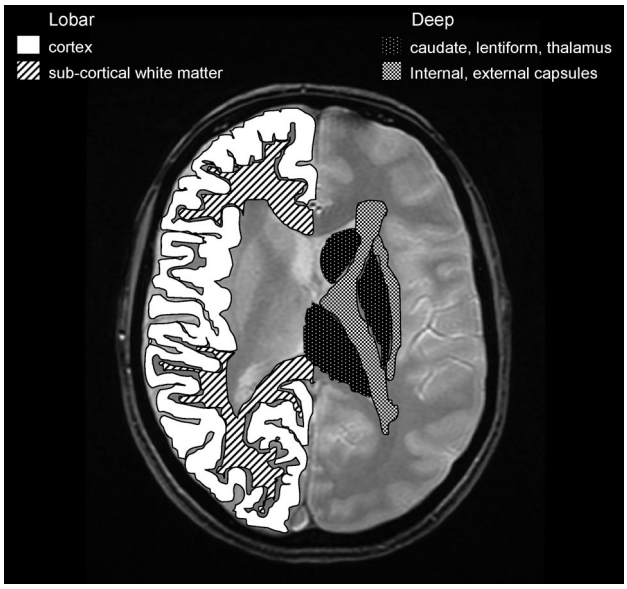

Figure 1. Diagram to illustrate the lobar and deep regions superimposed on a normal GRE MR brain examination. Solid white indicates lobar cortex; black and white stripes, subcortical white matter; black with white dots, deep caudate, lentiform, and thalamic nuclei; white with black dots, internal and external capsule.

presence/absence of ≥1 BMB improved using BOMBS when the analysis was restricted to certain BMBs, but remained similar to the pilot rating scale when considering certain and uncertain BMBs (Table 2). No significant difference in interrater reliability was discernible between brain locations using BOMBS (Table 2). The intraclass correlation coefficient for the overall number of certain BMBs was 0.93 (95% CI, 0.91–0.95). There were 27 definite BMBs observed by both raters in the same brain location, 25 of which were rated in the same size category (93%; 95% CI, 77–98); 2 BMBs were considered to be ≥5 mm by observer A, but <5 mm by observer B.

Discussion

With our simple pilot rating scale, we found that the assessment of BMBs on GRE T2* MR images in patients with stroke or TIA was not straightforward, with only moderate levels of interrater agreement, comparable to previous studies. BOMBS (Supplemental Figure I) improved interrater reliability when all brain locations were analyzed together, and particularly in lobar locations, which were identified in our pilot study as a difficult part of the brain to rate (Table 2). Although the consideration of BMB mimics is widely recognized as being important, observer variation persists, even when mimics are carefully thought about during MR scan review. BOMBS had its main effect by differentiating certain from uncertain BMBs; uncertainty about BMBs may be an important problem, because it applied to between one-third to one-half of BMBs in this study (Table 2).

BMB maximum diameters in previous research have varied from 2 to 5 mm, to ≤7 mm and ≤10 mm.[2] In this study, using a maximum diameter of 10 mm, we found few BMBs >5 mm in diameter, and we found only 2 disagreements about BMB size, but further studies are needed of observer agreement in BMB size categorization and of the pathological substrates for BMBs of varying sizes in different patient populations.

We found good agreement about the total number of BMBs. It is quite possible that the number of BMBs may influence their prognostic significance,[1] but this is not beyond doubt. On both these counts, continuing to collect the total number of BMBs rated by any observer—rather than subdividing a rating scale into no/few/many BMBs—will contribute to improving agreement about BMB number, as well as determining what the numeric thresholds for BMB prognostic/therapeutic significance are. Furthermore, studying observers' certainty in relation to their ratings of the presence/absence of BMBs as well as the number and size of BMBs seen will help in understanding whether small/uncertain BMBs are more likely to be counted in patients with multiple certain BMBs than those with a solitary certain BMB or multiple uncertain BMBs. BOMBS appeared to influence rater behavior in our study (Table 2); for example, observer A rated more BMBs than observer B in the pilot study, but this pattern was reversed with BOMBS.

Although studies have described the interrater reliability of BMB ratings (Table 1), we sought to improve agreement as our primary objective. We used κ and our study design fulfilled the assumptions inherent in the κ statistic: the subjects undergoing study and the observers were independent, and the categories in the scale were independent, mutually exclusive, and exhaustive.[18] The design of BOMBS benefited from the lessons gleaned using the pilot scale and independent review of the scans about which the observers disagreed. This study also benefited from using consistent imaging parameters and the same range of sequences (including GRE T2* in all), and blinding of each observer to the other's ratings.

The main weakness of this study was that these findings have not yet been validated in larger cohorts, in other disease groups, and among other observers. We encourage other researchers to do so to explore the generalizability of BOMBS. The influence of practice effects in our observers cannot be ruled out, but even before their ratings using the pilot rating scale both had experience of interpreting BMBs on MRI. The prevalence of BMBs appeared to decrease when BOMBS was validated, which was likely to have been related to the younger patients with milder strokes, whose MRI scans were used to test BOMBS, than those whose MRIs were used for the pilot rating scale; a systematic review has found BMB prevalence to be lower in these groups.[2] An artifact of the κ statistic is that it is affected in complex ways by the prevalence of the abnormality undergoing study, but a decrease in BMB prevalence from 20%–40% to 18%–25% is unlikely to have significantly biased the observers or affected the properties of the κ statistic.

The BOMBS dichotomization of BMBs into certain and uncertain was intended to improve agreement about the existence of certain BMBs. Prioritizing the identification of certain BMBs would result in improved specificity (at the

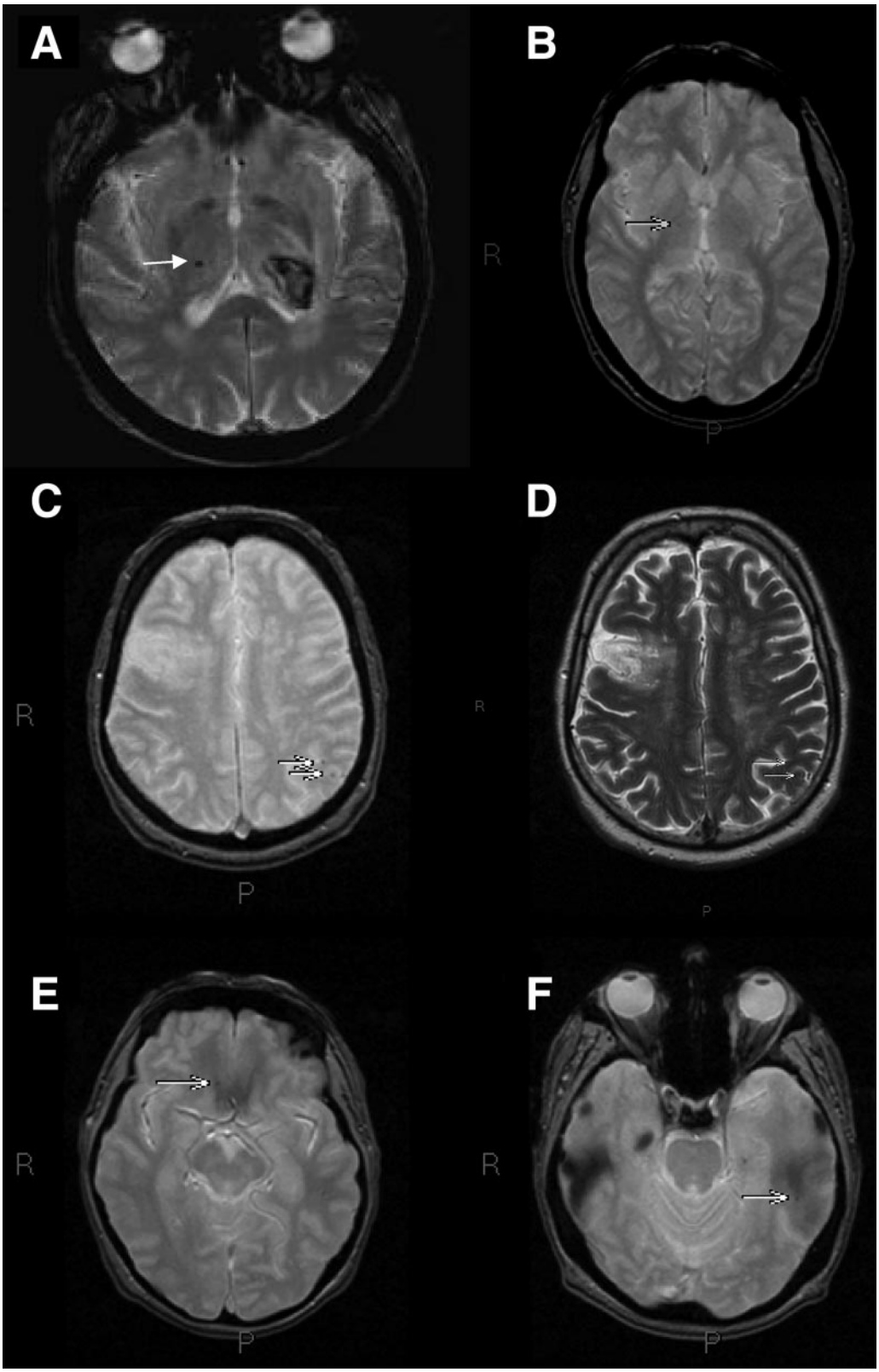

Figure 2. Examples of certain and uncertain BMBs, and BMB mimics. A, GRE T2* image showing a certain BMB in the right thalamus (arrow) in a patient with a left thalamic hemorrhage (not labeled). B, Uncertain BMB, GRE T2* image showing a pale lesion in the right thalamus (arrow). C and D BMB mimics. Small cortical vessels (arrows) in the left parietal lobe on GRE T2* (C) confirmed on T2 imaging (D) in this patient with a chronic right frontal cortical infarct (not labeled). E and F, BMB mimics. GRE T2* images showing partial volume artifact from right orbit (E, arrow) and left mastoid air cells (F, arrow).

expense of sensitivity) by identifying BMBs more reliably, which could improve the internal and external validities of research projects and encourage more reliable identification of BMBs should they become relevant in clinical practice. Investigators could also explore the robustness of their study findings using sensitivity analyses (by restricting analyses to either certain BMBs, or certain and uncertain BMBs, which would improve sensitivity at the expense of specificity). This dichotomization also permits the identification of a separate group of MRIs with uncertain BMBs to help improve understanding of why and how observers disagree about BMBs, and to follow-up such patients to determine if these uncertain BMBs mature into certain BMBs.

Our findings should be regarded as a baseline measure of observer agreement for future studies using BOMBS. Further work on ways of improving observer agreement about BMBs is needed, and training observers to recognize certain and uncertain BMBs, as well as their mimics, is an obvious priority (Figure 2). BOMBS will also enable others to study agreement about BMB size, number, brain location, and diagnostic certainty, as well as exploring the influence of these factors on the diagnostic and prognostic usefulness of BMBs.

Because the clinical implications of BMBs remain to be established, there is still an opportunity to improve the reliability of BMB assessments by the use (and further development) of the BOMBS rating scale, so that adequately powered, well-designed studies will be able to answer the outstanding clinical concerns about BMBs' diagnostic and prognostic value, and whether they should influence the prescription of antiplatelet, anticoagulant, or thrombolytic drugs. The use of a standard scale for BMBs is also essential for future studies to enable comparisons and meta-analyses.

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Disclosures

None.

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Associations of Clinical Stroke Misclassification ('Clinical-Imaging Dissociation') in Acute Ischemic Stroke

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Key Words
Acute ischemic stroke · Stroke subtype · Infarction · Acute stroke imaging · Diffusion-weighted imaging

Abstract
Background: Up to 20% of lacunar infarcts are clinically misdiagnosed as cortical infarcts and vice versa. The reasons for this discrepancy are unclear. We assessed clinical and imaging features which might explain this 'clinical-imaging dissociation' (C-ID). ***Methods:*** Patients with an acute stroke syndrome (cortical or lacunar) underwent magnetic resonance imaging including diffusion-weighted imaging (DWI). We recorded DWI-positive infarcts and proximity to cortex for small subcortical infarcts. We examined factors associated with C-ID. ***Results:*** 137 patients with a mild cortical or lacunar syndrome had an acute ischemic lesion on DWI. Of these, 21/93 (23%) with a cortical syndrome had an acute lacunar infarct and 7/44 (16%) with a lacunar syndrome had an acute cortical infarct. From 72 patients with an acute lacunar infarct on DWI, lesion proximity to cortex (odds ratio (OR) 14.5, 95% confidence interval (CI) 1.61–130.1), left hemisphere location (OR 8.95, 95% CI 1.23–64.99) and diabetes (OR 17.1, 95% CI 1.49–196.16) predicted C-ID. On multivariate analysis of all 137 patients, C-ID was associated with diabetes (OR 7.12, 95% CI 1.86–27.2). ***Conclusions:*** C-ID occurs in a fifth of patients with mild stroke. Lacunar infarcts lying close to cortex are more likely to cause cortical symptoms. Diabetes is associated with any clinical-imaging mismatch. Stroke misclassification which can arise with clinical classification alone should be minimized in research by verification with high-sensitivity imaging.

Introduction

Classification of acute ischemic stroke subtypes is important for categorizing patients into aetiologic and prognostic subgroups in clinical trials, epidemiological and pathophysiological studies, and may help guide patient management in clinical practice [1]. Although it is well established that infarcts in particular locations are associated with specific clinical symptoms, a proportion of patients with acute ischemic stroke will be incorrectly subtyped based on clinical assessment alone.

The Oxford Community Stroke Project (OCSP) clinical classification categorizes patients based on clinical assessment alone into those with a lacunar syndrome (LACS), a partial anterior circulation syndrome (PACS),

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Table 1. Previous studies identifying clinical-imaging dissociation (C-ID), and features examined

Reference	Setting	Brain imaging	Ischemic stroke subtype classification	LACS	LACS/large subcortical or cortical infarct (%)	Cortical syndrome	Cortical syndrome/ lacunar infarct (%)	Features examined in relation to C-ID
Lodder, 1994 [4]	Hospital	CT	–	147	23 (16)	203	19 (9)	Disability (OR 4.31, 95% CI 1.25–14.88) Leukoaraiosis (non-LACS; OR 3.79, 95% CI 1.32–10.05) Asymptomatic infarcts (non-LACS; OR 4.13, 95% CI 1.45–11.71) Hemisphere affected (non-LACS)
Al-Buhairi, 1998 [5]	Hospital	CT	OCSP	–	–	121	4 (5)	–
Pittock, 2003 [6]	Hospital	CT	OCSP	47	2 (10)	24	3 (11)	–
Wlodek, 2004 [7]	Hospital	CT	OCSP	101	29 (29)	193	29 (15)	–
Kobayashi, 2009 [8]	Hospital	CT	OCSP	60	19 (31)	183	3 (2)	–
Mead, 1999 [9]	Hospital	CT, MRI	OCSP	180	35 (19)	395	62 (16)	–
Mead, 2000 [3]	Hospital	CT, MRI	OCSP	144	35 (24)	298	38 (13)	Hemisphere affected (PACS, LACS)
Anderson, 2004 [10]	Hospital, community	CT, MRI	OCSP	69	12 (17)	75	16 (21)	–
Ay, 1999 [11]	Hospital	DWI	–	62	1 (2)	–	–	–
Lindgren, 2000 [12]	Hospital	DWI	–	23	2 (9)	–	–	–
Allder, 2003 [13]	Hospital	DWI	OCSP	–	–	42	6 (14)	Clinical severity (χ^2 18.9, $p < 0.01$)
Seifert, 2005 [14]	Hospital	DWI	OCSP	–	–	93[a]	14 (15)	–
Wessels, 2005 [15]	Hospital	DWI	–	73	13 (18)[b]	–	–	–
This study	Hospital	DWI	OCSP	80	7 (16)	136	24 (25)	Old infarcts (OR 3.02, 95% CI 1.06–8.59) Diabetes (OR 7.17, 95% CI 1.86–27.71)

PACS = Partial anterior circulation syndrome; LACS = lacunar syndrome; OCSP = Oxford Community Stroke Project; OR = odds ratio; CI = confidence interval; DWI = diffusion-weighted imaging; CT = computed tomography; MRI = magnetic resonance imaging.

[a] Patients with subcortical or brainstem lesions <1.5 cm in diameter.

[b] Four with single cortical lesion, 9 with scattered or multiple lesions containing a cortical lesion.

a total anterior circulation syndrome (TACS) or a posterior circulation syndrome (POCS) [2]. PACS and TACS both indicate cortical stroke syndromes. The OCSP classification can predict correctly the site and size of cerebral infarct, if visible, on computed tomography (CT) or magnetic resonance (MR) brain imaging in about three quarters of patients [3]. However, numerous studies demonstrate that about a fifth of patients with a cortical syndrome clinically have an acute lacunar infarct on imaging that accounts for their recent stroke symptoms; similarly some patients with LACS clinically have an acute cortical infarct on brain imaging that accounts for their recent stroke symptoms [4–15], creating a 'clinical-imaging dissociation' (C-ID) (table 1). This dissociation is important because epidemiological studies, primary treatment and secondary prevention trials in stroke have so far relied heavily on clinical classification so are likely to have incorporated 'noise' due to approximately one fifth of LACS and PACS patients being misclassified.

Several factors may contribute to C-ID. Previous studies suggested that the side of brain affected by stroke [3], leukoaraiosis [4], clinical severity [4, 13] and asymptomatic infarcts on imaging [4] were associated with C-ID. Other contributing factors have not been assessed. Delays in clinical assessment may allow neurological signs to resolve making an accurate history difficult to obtain (e.g. dysarthria and dysphasia can be difficult to distinguish on history alone); clinical examination may be insensitive to some subtle cortical signs (e.g. mild inattention) which would distinguish PACS from LACS. However, the one previous study that examined delay to diagnosis did not find any association with C-ID [3]. Reliability of classification is affected by observer expertise in use of the OCSP classification, particularly in minor stroke [16]. C-ID may also arise when there is failure of brain imaging to ascertain relevant ischemic lesions, either because the imaging is relatively insensitive to small acute lesions [17] or is performed too late to identify the acute lesion reliably.

Small subcortical infarcts are considered to cause their symptoms because their location in the subcortical white matter or basal ganglia effectively disconnects a larger section of cortex than is affected by an equivalent-sized lesion in the cortex (fig. 1). We hypothesized that a small subcortical infarct lying close to the cerebral cortex could mimic symptoms of a mild cortical syndrome (PACS) by causing functional disconnection of only a small area of cortex compared to one of the same size lying in the periventricular white matter or basal ganglia which would disconnect a larger area of cortex. We also considered that other factors, such as previous stroke, could increase the proportion with C-ID, as residual features of a previous stroke could make interpretation of features due to the acute stroke difficult, and that common stroke risk factors might influence symptomatology.

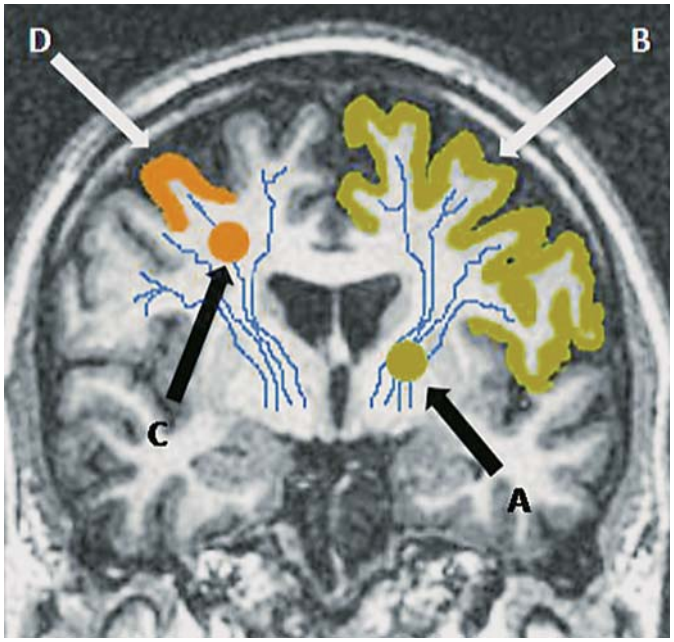

Fig. 1. Coronal T_1-weighted MRI brain to demonstrate how the site of a small subcortical (lacunar) infarct could influence clinical presentation. A small subcortical infarct lying in the left internal capsule, i.e. deep white matter (A), would cause functional disconnection of a large area of cortex (B, shaded). A peripheral small subcortical infarct lying close to cortex (C) would affect only a limited area of cortex (D, shaded), and could mimic a mild cortical stroke.

Methods

We included patients from a prospectively collected hospital-based stroke register of consecutive stroke and transient ischemic attack (TIA) patients seen at a large academic teaching hospital between April 2002 and May 2005. In the present study we included only those patients who underwent brain MR imaging (MRI). We performed MR when time from stroke onset was greater than 5–7 days or uncertain, if there was clinical uncertainty about the definite diagnosis of stroke (particularly in patients with prior stroke) or of the vascular territory involved (carotid or vertebrobasilar), if there was a potential underlying cause of stroke that required further investigation by advanced brain imaging, or if the patient was suitable for inclusion into other studies of large artery or subcortical stroke requiring brain MRI.

All patients were assessed by an experienced stroke physician who took a detailed history, performed a general and neurological examination and recorded the National Institutes of Health Stroke Scale score. Patients were assigned a clinical subtype according to the OCSP classification based on the maximum stroke deficit as described previously [1]. Lacunar and mild cortical syndromes (LACS and PACS, respectively) were defined according to the OCSP classification [1]. LACS was defined as one of the classical LACSs – i.e. pure motor weakness and/or sensory loss of face and arm, arm and leg or all three, or ataxic hemiparesis (ipsilateral corticospinal and cerebellar-like dysfunction without other features clearly localizing to the posterior circulation, including dysarthria-clumsy hand syndrome and homolateral ataxia and crural paresis) – in the absence of visual field defect or higher cerebral dysfunction. In patients with faciobrachial or brachiocrural motor and/or sensory deficits, only involvement of the whole limb was considered acceptable for LACS; patients with involvement of less than the whole limb were classified as PACS. Mild cortical stroke syndrome (PACS) was defined as a maximum clinical deficit of either: weakness or sensory loss in the face, arm or leg; loss of higher cerebral function (e.g. dysphasia or neglect); or weakness in more than one limb in the presence of loss of higher cerebral dysfunction or homonymous hemianopia. Isolated homonymous hemianopia was classified as POCS [1], a relatively crude grouping of posterior circulation cortical and lacunar lesions with clinical consequences which are generally less predictable because of the greater frequency of developmental vascular anomalies and greater variability of the territory supplied by individual arteries.

All patients had MRI including diffusion-weighted imaging (DWI), carotid Doppler ultrasound, electrocardiogram, blood tests, and other investigations as indicated. We recorded risk factors including diabetes mellitus (defined as having a previous diagnosis of, or being on current medication for, diabetes), hypertension (defined as having a history of hypertension requiring medication) and prior history of stroke (i.e. clinical presentation with stroke). The Edinburgh Stroke Study was approved by the Local Research Ethics Committee and all patients (or their relatives) gave written informed consent. Patients underwent 1.5 T MRI (GE Signa LX EchoSpeed scanner, Milwaukee, Wisc., USA). We collected sets of axial diffusion-weighted echo planar (EP) images (sensitization levels b = 0 and 1,000 s/mm^2) with 5-mm slice thickness, 1-mm slice gap, 128 × 128 image matrix and 24 × 24 field of view. Other MR parameters have been published elsewhere [18]. Images were reviewed by a neuroradiologist (G.P.), blinded to all clinical details. Location and size of recent infarcts were recorded. Recent infarcts were defined as hyperintense on DWI, hypointense on the apparent diffusion coefficient map and either normal or hyperintense to normal brain on fluid-attenuation inversion

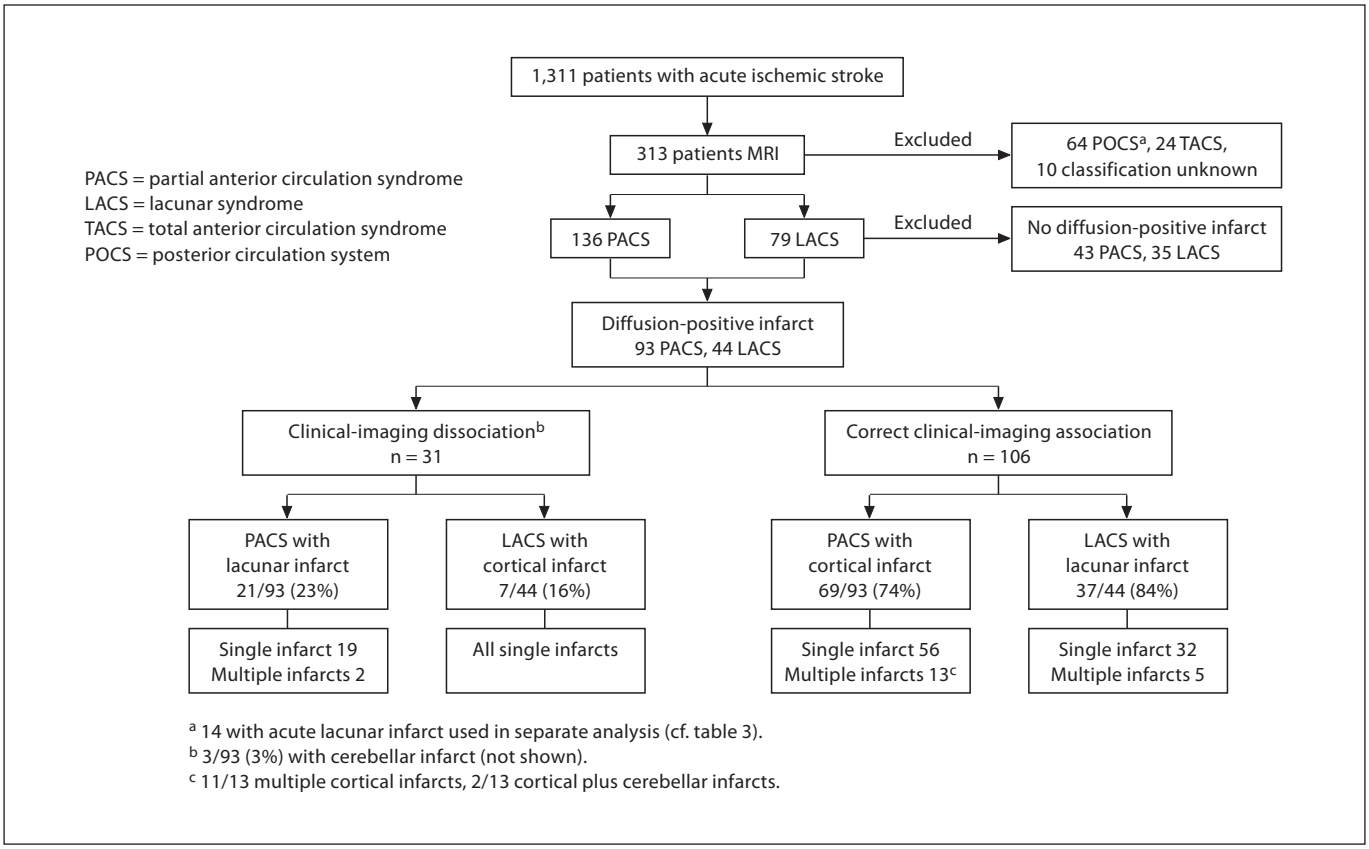

Fig. 2. Identification of patients with PACS and LACS for assessment of C-ID and imaging findings.

recovery (FLAIR)/T_2-weighted imaging (less hyperintense than cerebrospinal fluid on T_2). Lacunar infarcts were defined as round or ovoid lesions measuring ≤20 mm in maximal diameter in the white matter, basal ganglia or brainstem. Proximity to cortex of recent lacunar infarcts was noted on any sequence on which the infarct was visible. We defined 'close to cortex' as the edge of the infarct lying within 2 mm of the cortical margin in the white matter. Infarcts were defined as cortical where there was a typical configuration with involvement of cortex ± adjacent white matter, and striatocapsular where located in the basal ganglia or centrum semiovale and measuring ≥20 mm. Uncertain lesions were checked with a second neuroradiologist (J.W.). A lacunar infarct was considered 'appropriate' in patients presenting with LACS; a lacunar infarct in the brainstem or thalamus, i.e. in the vertebrobasilar territory, was also considered 'appropriate' to POCS. A small- or medium-sized cortical infarct was considered 'appropriate' in PACS. We also recorded white matter hyperintensities (WMH) (0–3 on the Fazekas scale [19]); old strokes using all sequences; enlarged perivascular spaces (EPVS, defined as ≤2 mm round or linear isointense to cerebrospinal fluid lesions along the course of penetrating arteries, T_2-hyperintense and T_1/FLAIR-hypointense) in the basal ganglia and centrum semiovale (0–4 on a local scale, where 0 = none and 4 = >40) [20] and atrophy (0–3 on a validated scale, where 0 = none and 3 = severe) [21].

Statistical Analysis

We assessed the statistical significance of differences in baseline characteristics and brain-imaging features using Student's t test for continuous variables, the Mann-Whitney test for non-normally distributed continuous variables, and the χ^2 test for dichotomous variables. We performed multivariable analyses using logistic regression to determine independent factors for C-ID. In the logistic regression model we included all variables from univariate analysis and obtained adjusted odds ratios (OR) (comparing patients with C-ID versus those without) and 95% confidence intervals (CIs). We dichotomized scores for WMH (0–1 vs. 2–3), brain tissue loss (0–1 vs. 2–3) and EPVS (0–1 vs. 2–4) due to low frequencies. We performed analyses with Minitab Statistical Software Version 15 (Minitab, Inc., State College, Pa., USA).

Results

Amongst the 1,311 acute ischemic stroke patients recruited to the Edinburgh Stroke Study, 313 underwent MR brain imaging, of whom 136 (43%) presented clinically with PACS, 79 (25%) with LACS, 24 (8%) with TACS,

Table 2. Factors associated with clinical-imaging dissociation (C-ID) in patients with PACS and LACS and an acute infarct on DWI

	C-ID (n = 31)	No C-ID (n = 106)	Univariate statistic and test score	Univariate p value	Multivariate p value	Multivariate OR (95% CI)
Demographics						
Age, years	71 ± 11	70 ± 13	Student's t test –0.4	0.69	0.1	1.04 (0.98–1.10)[1]
Gender, male	19 (61)	64 (60)	χ^2 0.008	0.93	0.74	1.21 (0.40–3.70)
Medical history						
Previous stroke, %	12 (39)	24 (23)	χ^2 3.03	0.08	0.14	2.38 (0.74–7.60)
Hypertension, %	23 (74)	58 (56)	χ^2 3.52	0.06	0.88	1.09 (0.36–3.34)
Diabetes, %	9 (29)	6 (6)	χ^2 11.2	0.001	0.004	7.12 (1.86–27.2)
Clinical						
Median days, onset to assessment	16	11	Mann-Whitney 5 (0–12)	0.09	0.72	1.01 (0.96–1.07)
Range (IQR)	0–97 (10–23)	0–125 (1–22)				
Median days, onset to MRI	21	15	Mann-Whitney 8 (0–14)	0.05	0.71	1.01 (0.9–1.06)
Range (IQR)	0–97 (14–33)	0–140 (1–31)				
MR brain imaging characteristics						
Left hemisphere, %	17 (55)	61 (58)	χ^2 0.07	0.79	0.49	1.44 (0.51–4.09)
WMH 2–3, %[a]	16 (53)	39 (37)	χ^2 2.62	0.12	0.85	1.12 (0.35–3.55)
EPVS 2–4, %[b]	19 (63)	41 (340)	χ^2 5.2	0.02	0.38	1.61 (0.56–4.60)
Brain tissue loss 2–3, %[c]	8 (28)	29 (28)	χ^2 <0.001	1.0	0.1	0.33 (0.09–1.24)
Old stroke lesions, %	20 (65)	45 (42)	χ^2 5.49	0.02	0.08	2.56 (0.89–7.36)

EPVS = Enlarged perivascular spaces; WMH = white matter hyperintensities; IQR = interquartile range; OR = odds ratio; CI = confidence interval.
[1] Odds ratio (OR) per additional year of age. [a] On Fazekas scale. [b] On EPVS scale. [c] On brain tissue loss scale.

64 (21%) with POCS, and 10 (3%) with an uncertain OCSP classification (fig. 2). Ninety-three (68%) of 136 patients with PACS and 44/79 (56%) patients with LACS had a diffusion-positive infarct relevant to the clinical presentation (fig. 2). Six (4%) patients with PACS and 3 (4%) LACS in whom DWI was normal had lesions on other sequences as the likely cause of symptoms. Patients undergoing MRI were slightly younger when compared with the 1,311 ischemic stroke patients from which we identified our study population, with a higher proportion of males and a lower prevalence of diabetes but the proportion of PACS and LACS were similar (online suppl. table 2, www.karger.com/doi/10.1159/000286342).

Sixty-nine (74%) patients presenting with PACS had an acute cortical infarct (all small- or medium-sized and considered appropriate to clinical syndrome) (fig. 2), 21 (23%) had an acute lacunar infarct (fig. 2), and 3 (3%) had a cerebellar infarct on DWI. Of patients presenting with LACS, 37/44 (84%) had an acute lacunar infarct and 7 (16%) had an acute cortical infarct. Most acute lacunar infarcts identified on DWI in patients presenting with LACS or PACS were located in the centrum semiovale (18/37 LACS, 20/21 PACS). Amongst patients with an acute infarct on DWI, 65/138 (47%) patients had old infarcts on imaging, the median WMH score was 1.62 (range 0–3) and the median EPVS score was 2 (range 0–4).

In the cohort of 137 patients with PACS and LACS and an acute infarct on DWI, C-ID was associated on univariate analysis with diabetes (p = 0.001), increasing time from onset of stroke symptoms to MRI (p = 0.05), EPVS (p = 0.02) and old stroke lesions on brain imaging (p = 0.02), but not with age (p = 0.69), history of previous stroke (p = 0.08), brain tissue loss (p = 1.0) or WMH (0.12; table 2). On multivariate analysis, diabetes (OR 7.12, 95% CI 1.86–27.2; p = 0.004) was independently associated with C-ID.

Multiple acute infarcts were not associated with C-ID either: amongst 44 LACS, 5 (11%) had multiple DWI-positive infarcts (all lacunar lesions) and none had C-ID. Amongst 93 PACS, 15 (16%) had multiple DWI-positive infarcts, of whom 2 (13%) had C-ID (all multiple lacunar infarcts) and 13 (87%) were correctly associated (showing multiple cortical, or cortical plus cerebellar, infarcts; fig. 2).

We examined characteristics associated with a lacunar infarct causing PACS clinical syndrome in all 72 patients with an acute lacunar infarct on DWI. Thirty-seven (51%) patients presented with LACS, 21 (29%) with PACS, and 14 (20%) with POCS (fig. 2). Lacunar infarcts in POCS patients were located (appropriate to symptoms) in the posterior circulation territory (12 brainstem, 1 thalamus, 1 posterior border zone) and were therefore not considered to have C-ID. C-ID was associated in univar-

Table 3. Associations with clinical-imaging dissociation (C-ID) in all subjects with an acute lacunar infarct on DWI (n = 72)

	C-ID (n = 22)	No C-ID (n = 50)	Univariate statistic and test score	Univariate p value	Multivariate p value	Multivariate OR (95% CI)
Demographics						
Age, years	75 ± 10	69 ± 11	Student's t test –2.33	0.03	0.01	1.16 (1.03–1.30)[1]
Gender, male (%)	14 (64)	27 (54)	χ^2 0.58	0.45	0.09	5.25 (0.78–35.41)
Medical history						
Previous stroke, %	6 (27)	8 (16)	χ^2 1.24	0.27	0.64	1.66 (0.20–13.82)
Hypertension, %	18 (82)	22 (44)	χ^2 8.85	0.004	0.12	3.72 (0.72–19.28)
Diabetes, %	6 (27)	4 (8)	χ^2 4.75	0.06	0.02	17.1 (1.49–195.16)
Clinical						
Median days, onset to assessment	18	14	Mann-Whitney –6	0.04	0.49	1.05 (0.91–1.21)
Range (IQR)	1–97 (14–23)	0–134 (3–22)				
Median days, onset to MRI	27	20	Mann-Whitney –6	0.04	0.76	0.98 (0.84–1.13)
Range (IQR)	6–97 (16–32)	0–141 (6–29)				
MR brain imaging characteristics						
Subcortical infarct close to cortex, %	16 (73)	15 (30)	χ^2 11.4	0.001	0.02	14.5 (1.61–130.1)
Infarct size, mm	11.7 ± 3.4	10.8 ± 4.3	Student's t test –1.01	0.32	0.99	1.00 (0.82–1.23)
Left hemisphere location, %	15 (68)	26 (52)	χ^2 1.22	0.27	0.03	8.95 (1.23–64.99)
WMH 2–3, %[a]	12 (55)	20 (40)	χ^2 1.31	0.25	0.43	0.48 (0.08–2.93)
EPVS 2–4, %[b]	14 (64)	25 (49)	χ^2 0.98	0.32	0.67	1.52 (0.22–10.46)
Brain tissue loss 2–3, %[c]	7 (32)	9 (18)	χ^2 1.69	0.19	0.35	0.30 (0.02–3.75)
Old stroke lesions, %	14 (64)	23 (46)	χ^2 1.9	0.17	0.13	0.20 (0.02–1.65)

EPVS = Enlarged perivascular spaces; WMH = white matter hyperintensities; IQR = interquartile range; OR = odds ratio; CI = confidence interval.
[1] Odds ratio (OR) per additional year of age. [a] On Fazekas scale. [b] On EPVS scale. [c] On brain tissue loss scale.

iate analyses with increasing age (p = 0.03), hypertension (0.004), increasing delay from symptom onset to clinical examination (p = 0.001) and to MRI (p = 0.04) and infarct positioned close to cortex (p = 0.001) (table 3). In multivariate analysis, closeness to cortex (OR 14.5, 95% CI 1.61–130.1; p = 0.02) and older age (OR 1.16, 95% CI 1.0–1.30; p = 0.01) remained independently associated with C-ID; diabetes (OR 17.1, 95% CI 1.49–195.16; p = 0.02) and left-hemispheric location (OR 8.95, 95% CI 1.23–64.99; p = 0.03) were also independent associates. There was no difference in the size of the lacunar infarcts between those causing PACS and those causing LACS clinical syndromes (mean 11.7 ± 3.4 vs. 10.8 ± 4.3 mm; p = 0.32; table 3), nor in the size of those lacunar infarcts that were close to cortex and caused PACS (n = 16) or LACS (n = 15) (mean 12.3 ± 5.3 vs. 12 ± 3.7 mm; p = 0.8).

Discussion

In our study of acute stroke patients with PACS and LACS and an acute infarct on DWI, we found that 23% of patients presenting with PACS had an acute lacunar infarct, and 16% of patients presenting with LACS had an acute cortical infarct and no other explanation for their recent stroke symptoms. The main factors associated with C-ID amongst all patients in this study, after adjusting for potential confounders, was diabetes (old stroke lesions and previous history of stroke were associated in univariate analysis only), and in patients with an acute lacunar infarct on imaging, proximity of the lacunar infarct to the cortex, older age, diabetes and left hemisphere location. Lesion size, multiple acute infarcts, time to scanning, WMH, brain atrophy and history of prior stroke were not associated with C-ID.

The present study has some methodologic strengths. We performed a more comprehensive examination of associated features than in previous studies of C-ID. We identified consecutive stroke and TIA patients presenting to our stroke service. Patients undergoing MRI had similar proportions of PACS and LACS to the registry cohort as a whole. The minor differences between patients undergoing MRI and those that did not (slightly younger, more males, fewer with vascular risk factors) is unlikely to have influenced the generalizability of our results. All patients were very carefully examined by an experienced stroke physician and categorized according to strict interpretation of the OCSP criteria. Images were reviewed systematically according to a structured proforma by a trained rater using validated scales.

There are limitations of our study. Overall, only 313/1,311 (24%) of patients presenting with acute stroke underwent MRI, which may have introduced a selection bias. Other factors which may have led to selection bias were the inclusion of patients with increasing delay, or uncertain time, since stroke onset, and where there was clinical uncertainty about stroke diagnosis. Our sample may therefore have included an overrepresentation of patients who were more difficult to subtype. However, this does not negate the observation that lacunar lesion location was associated with C-ID. Median time from stroke onset to MRI of 19 days (many were outpatients, with mild stroke), i.e. outside the time period generally considered optimal for DWI, and only 64% (137/215) patients had a diffusion-positive infarct. However, a previous study showed no difference in the proportion with an acute infarct on DWI in those scanned before versus after 4 weeks [22]. Although several patients had DWI outside the optimal time period, previous work has shown that DWI may also be useful up to several weeks after stroke onset [23]. We also cannot exclude the possibility that the infarct responsible for initial symptoms was no longer visible on DWI by the time the patient underwent brain imaging, and that a new, silent DWI infarct (but sufficiently consistent with the infarct location as suggested by the symptoms and signs as to be considered as the acute index infarct) had appeared in this period, but this possibility was considered to be low and consequently not a significant confounding factor. We did not investigate underlying mechanisms as a cause of C-ID, and the study was not designed to test the effect of clinician experience on misdiagnosis, a factor identified in one previous study [16].

Previous studies did not consider proximity of lacunar infarcts to cortex or diabetes as possible factors for C-ID. The association with diabetes may be partly explained by a co-association with old 'silent' infarcts; however, although old infarcts were associated with C-ID in univariate analysis, they did not remain independently associated in multivariate analysis, as found previously [4]. Assigning clinical subtype may be more difficult in the presence of an old infarct, even if clinically silent, as signs from the previous infarct may confuse the clinical picture. The association of left hemisphere location and C-ID is consistent with previous studies which found that left-sided lesions were more common in patients with PACS/non-LACS with C-ID [4] and that right-sided lesions were more common in LACS presenting with C-ID [3]. This may be explained by the difficulty in distinguishing dysarthria from dysphasia, especially if symptoms and signs were mild or had resolved by the time of assessment. We did not find an association between C-ID and WMH, in contrast to one previous study [4], possibly because the latter used CT, which is less sensitive to WMH than MR FLAIR or T_2. We found that 11% of patients with LACS had multiple acute lacunar infarcts, similar to previous studies [11, 14, 15], but multiplicity of infarcts did not contribute to C-ID. We did not find an association between time lapse from stroke onset to MRI and C-ID, in agreement with one previous study using CT [3]. Ability to recall symptoms and signs may deteriorate with increasing time to assessment, particularly with speech disorders. Others have reported problems with very early or very late diagnosis of lacunar stroke [24]. Our use of maximum deficit in assigning the OCSP subtype may have overcome any effect of time on stroke diagnosis.

C-ID has important implications for research into epidemiology, pathophysiology and treatment of lacunar stroke as well as for clinical practice. In research which relies heavily on clinical presentation alone, results may be affected by 'noise' caused by C-ID of between 10 and 20% patients with mild stroke. Studies in which CT is used in conjunction with clinical classification will also be affected, since CT is less sensitive than DWI for small acute infarcts [17], particularly when performed soon after symptom onset, as is increasingly the case. Acute ischemic stroke lesions are visible on CT in <20% of LACS and <35% PACS (i.e. mild stroke) at <3 h, rising to approximately 45 and 60% at 36 h [25]. The debate over mechanisms of lacunar stroke – up to 20% are said to be associated with cardiac and large artery atherothromboembolism [26, 27] rather than intrinsic small vessel disease – could be explained by C-ID. Similarly, large primary and secondary prevention trials of ischemic stroke testing aspirin, cholesterol-lowering drugs and antihypertensives have relied heavily on clinical classification and CT [28]. 'Noise' from C-ID may have impeded the demonstration of any difference in treatment effects between stroke subtypes, if one existed. In future, where precise diagnosis of stroke subtype and lesion location is important, lesion location should be verified by sensitive imaging.

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Counting Cavitating Lacunes Underestimates the Burden of Lacunar Infarction

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Background and Purpose—On brain imaging, lacunes, or cerebrospinal fluid–containing cavities, are common and are often counted in epidemiological studies as old lacunar infarcts. The proportion of symptomatic lacunar infarcts that progress to lacunes is unknown. Noncavitating lacunar infarcts may continue to resemble white matter lesions.

Methods—We identified patients with acute lacunar stroke, with or without an acute lacunar infarct on computed tomography or MRI, who had follow-up imaging. A neuroradiologist classified lacunar infarcts progressing to definite or possible cavities on follow-up imaging. We tested associations between cavitation and patient-related, stroke-related, and imaging-related features, including other features of small vessel disease.

Results—Among 90 patients (mean age 67 years), any cavitation was present on follow-up imaging in 25 (28%), and definite cavitation in 18 (20%). Definite cavitation was associated with increasing time to follow-up imaging (median 228 days, range 54 to 1722, versus no cavitation 72 days, range 6 to 1440; $P=0.0003$) and deep cerebral atrophy ($P=0.03$) but not with age, stroke severity, larger initial infarct size, or other features of small vessel disease. Hypertension and diabetes were negatively associated with cavitation ($P=0.01$ and 0.02, respectively).

Conclusions—Definite cavitation occurs in one fifth of symptomatic lacunar ischemic strokes, implying that most continue to resemble white matter lesions. Epidemiology and pathophysiology studies of lacunar stroke, which have only counted lacunes as lacunar infarcts, may have substantially underestimated by as much as 5 times the true burden of lacunar stroke disease. **(*Stroke*. 2010;41:267-272.)**

Key Words: brain imaging ■ lacunar infarction ■ lacunes ■ epidemiology

A lacune is commonly defined as a small, deep, 3- to 20-mm (or in some cases, 3- to 15-mm) cerebrospinal fluid (CSF)–containing cavity. The term lacune was first used by Dechambre in 1838[1] and later in 1901 by Marie,[2] who suggested these could be attributable to infarcts. Sixty years later, Fisher defined lacunes pathologically as infarcts, either clinically silent or symptomatic, resulting from occlusion of a penetrating branch of a cerebral artery.[3–5] The term lacune is often used interchangeably with the terms lacunar infarct and lacunar stroke. Tissue loss replaced by CSF (or near-CSF) is also known radiologically as cerebromalacea and can affect gray or white matter, but this term is usually applied to cortical infarcts.

Silent lacunes (on imaging or histopathology, without clear evidence of relevant stroke symptoms) are often termed silent lacunar infarcts or silent brain infarcts. Silent lacunes are frequently seen in healthy older people, occur in 8% to 28% of the general population, are associated with increasing age, hypertension, and subtle deficits in physical and cognitive function, and more than double the risk of stroke and dementia.[6] In most studies of silent brain infarcts, there is no definitive pathological evidence that the lesion was attributable to infarction.

The association between clinically evident lacunar ischemic stroke and silent lacunes is unclear because the proportions in whom the symptomatic lacunar infarct progresses to a cavity and in whom the lesion continues to resemble a white matter lesion are unknown. This has significant implications for epidemiology (including risk factor) and pathogenesis studies of lacunar infarction and cerebral small vessel disease, in which it is common practice to count lacunes and only consider these as silent lacunar infarcts, omitting to correlate these with symptoms.

We investigated the proportion of symptomatic lacunar strokes progressing to lacunes and assessed patient-related, stroke-related, and imaging-related associations of cavitation.

Subjects and Methods

We identified patients with acute lacunar ischemic stroke, diagnosed after clinical and radiological evaluation, with baseline and follow-up MRI or computed tomography (CT) brain imaging, from 2 studies: a

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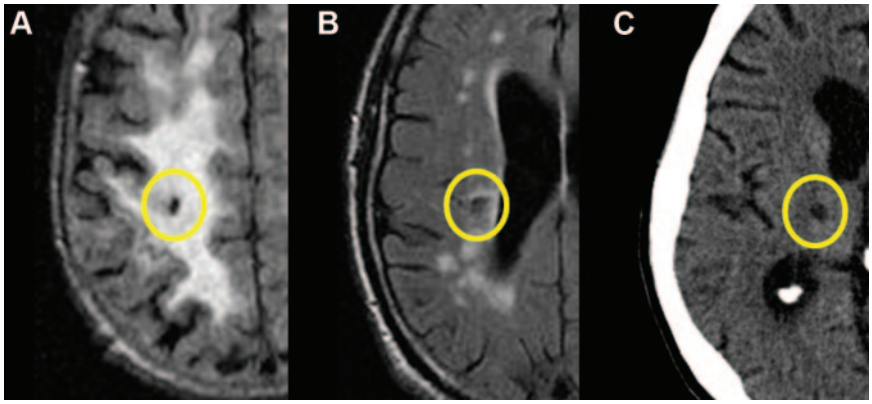

Figure 1. Examples of definite (A) and possible (B) cavities in the centrum semiovale on FLAIR MRI, both with concomitant WML. C, Cavity in the right thalamus on CT.

prospective register of consecutive stroke patients presenting to an academic teaching hospital,[7] and a prospective study of acute lacunar stroke.[8] A stroke physician assigned a classification using the Oxfordshire Community Stroke Project Classification,[9] measured the National Institutes of Health Stroke Scale score (NIHSS), and assessed vascular risk factors. Written consent was obtained from all patients. Both studies were approved by the local research ethics committee.

We included patients with baseline imaging with either MRI (diffusion-weighted imaging [DWI], T2-weighted imaging, and fluid-attenuated inversion recovery [FLAIR]) or CT brain imaging. We included patients with or without an acute lacunar infarct on MRI (because the high sensitivity of magnetic resonance enabled us to exclude as fully as possible patients with cortical infarction), but on CT, we only included patients with a visible recent lacunar infarct in the appropriate area for symptoms (because the low sensitivity of a negative CT would not allow us to exclude cortical stroke, which may give rise to lacunar-type symptoms).[10] Baseline and follow-up imaging was with either MRI (including T1-weighted, T2-weighted, FLAIR, and gradient echo sequences) or CT (parameters published previously).[7,8] Patients with baseline DWI-positive MRI and follow-up MRI were considered to represent a "pure" subgroup because diagnosis was most sensitive and specific for stroke subtype. The inclusion of the larger group in whom baseline imaging was either CT positive or magnetic resonance negative enabled us to increase sample size, study power, and generalizability.

A neuroradiologist (G.M.P.) recorded site and diameter of the acute index symptomatic lacunar infarct, white matter lesions (WML), enlarged perivascular spaces, cerebral atrophy, lacunes (separate from index lesion), and spongiform lesions (separate from index lesion). Acute lacunar infarcts were defined as round or ovoid lesions of increased signal relative to white matter on DWI, FLAIR, or T2-weighted imaging, or decreased attenuation relative to white matter on CT, 3 to 20 mm in diameter, in the white matter, basal ganglia, or brain stem. WMLs were rated on MRI (0 to 3 on Fazekas scale[11]) or CT (0 to 2 on van Swieten scale[12]). Enlarged perivascular spaces, defined as ≤2 mm round or linear CSF–isointense lesions along the course of penetrating arteries, were rated on MRI in the basal ganglia and centrum semiovale[13] (0 to 4, where 0=none, 1=<10, 2=<20, 3=20 to 40, and 4=>40); atrophy was also rated (0 to 3 on validated scale,[14] where 0=none and 3=severe). Lacunes were defined as round or ovoid lesions of CSF attenuation/signal measuring 3 to 20 mm in the white matter, basal ganglia, or brain stem; correlation with appropriate symptoms was not sought. Coding was performed unblinded to clinical symptoms (to be certain of correct identification of the index lesion) but blind to all other clinical data.

At follow-up, a "definite" cavity was defined as a lesion of CSF, or near-CSF, attenuation on CT, or of CSF signal on T2-weighted imaging or FLAIR MRI, at the site of the index infarct (Figure 1). A "possible" cavity was defined on FLAIR as a lesion of spongiform appearance with areas of marked hypointensity showing early confluence at the site of the index infarct. "Definite" (CT and MRI) and "possible" cavitation (FLAIR only) were considered together as "any evidence of cavitation." In cases of uncertainty, images were reviewed by a second experienced neuroradiologist (J.M.W.). Lacunes developing elsewhere in the brain between baseline and follow-up imaging were also recorded; correlation with appropriate symptoms was not sought for these lesions.

Statistical Analysis

We calculated proportions with any evidence of, and definite, cavitation (with 95% CIs) in the whole group, the "pure" subgroup and the subgroup with an index infarct. We assessed statistical significance of differences in baseline characteristics and imaging features in patients with "definite" and any ("definite" plus "possible") cavitation of the index lacunar infarct in the whole group and "pure" subgroup. We used the Student *t* test for continuous variables, the Mann–Whitney *U* test for non-normally distributed continuous variables, and the χ^2 test for dichotomous variables. We performed multivariate analysis using logistic regression to determine independent predictors of cavitation, allowing one variable per 5 outcome events. We obtained adjusted odds ratios (ORs) and 95% CIs, comparing patients with "any" and "definite" cavitation versus those without. For "any" cavitation, we used significant variables from univariate analysis (hypertension, diabetes, time to follow-up), and concomitant lacunes at baseline and deep atrophy, considered more likely than other features to be associated with cavitation; for "definite" cavitation, we included time to follow-up (significant on univariate analysis), hypertension (significant in univariate analysis for "any" cavitation), and deep atrophy. We dichotomized scores for WMLs (Fazekas 0 to 1 versus 2 to 3; van Swieten 0 versus 1 to 2), brain tissue loss, and enlarged perivascular spaces (0 to 2 versus 3 to 4) attributable to low frequencies. We also examined the proportion with any progression of cavitation of existing "spongiform" nonindex lesions. All statistical analyses were performed using Minitab (Version 15; Minitab Inc).

Results

Ninety patients met our inclusion criteria. Mean age was 67±12 years, 48 (53%) had a history of hypertension, 18 (20%) diabetes, and 12 (13%) a history of previous stroke. A "pure" subgroup of 47 of 90 (52%) patients had a DWI-positive acute lacunar infarct and follow-up MRI (Table 1); 6 had baseline MRI and follow-up CT; and 21 had baseline CT with either CT or MRI follow-up.

Of the 74 of 90 (82%) patients with an acute index lacunar infarct, 45 (60%) were in the centrum semiovale, 18 (24%) in the internal capsule, 9 (12%) in the thalamus, and 3 (4%) in the brain stem. Of the 16 of 90 MRI-negative patients, follow-up MRI was normal in 15 and showed a noncavitating lesion in an appropriate site for original symptoms in one (Table 1).

On follow-up imaging, 18 of 90 (20%; 95% CI, 12% to 28%) patients showed definite, and a further 7 possible, cavitation, making a total of 25 of 90 (28%; 95% CI, 19% to 37%) with any evidence of cavitation. In the "pure" sub-

Table 1. Type of Brain Imaging, Including Follow-Up Appearance of Symptomatic Lacunar Infarct (n=90)

Type of Imaging		Baseline DWI		Infarct Visible at Follow-Up		Cavitation of Infarct at Follow-Up		
Baseline	Follow-Up	Lesion	n	Yes	No	None	Possible	Definite
MRI	MRI	Yes	47*	47	0	33	7	7
MRI	CT	Yes	6	6	0	4	n/a	2
MRI	MRI	No	16	1	16	1	0	0
CT	MRI	n/a	10	9	1	6	0	3
CT	CT	n/a	11	11	0	5	n/a	6

*"Pure" subgroup.

group, 7 of 47 (18%) had definite cavitation, and an additional 7 showed possible cavitation, making a total of 14 of 47 with any evidence of cavitation (30%; 95% CI, 17% to 43%). In sensitivity analyses to exclude patients without a DWI-positive lesion at baseline (ie, 74 patients with visible lacunar infarction), definite cavitation was visible in 18 (24%; 95% CI, 15% to 34%), and possible cavitation in an additional 7. Therefore, 25 of 74 (34%; 95% CI, 23% to 45%) showed any evidence of cavitation. In one case, an acute lacunar infarct on baseline CT was not visible on follow-up MRI.

In the entire group of 90 patients, cavitation was associated with increasing time to follow-up imaging in those with both definite and any evidence of cavitation on univariate analysis ($P=0.0003$ and $P=0.03$, respectively; Tables 2 and 3) and with deep atrophy in patients with definite cavitation ($P=0.03$). Figure 2 shows the time from stroke onset to follow-up imaging in patients with any evidence of, and definite, cavitation. In patients with any evidence of cavitation, hypertension and diabetes were negatively associated with cavitation ($P=0.01$ and 0.02, respectively). In multivariate analysis, increasing time to follow-up and deep atrophy remained significant for patients with definite cavitation (OR, 1.81; 95% CI, 1.12% to 2.92% and OR, 3.24; 95% CI, 1.02% to 10.27%). No other patient-related, stroke-related, or imaging-related variables (age, NIHSS, and all

Table 2. Clinical and Imaging Associations of Cavitation in Patients With Any Evidence of Cavitation (n=90)

		Any Evidence of Cavitation			
	n Where Not 90	Yes n=25	No n=65	Test	*P* Value
Demographics					
Age in years (mean±SD)		68.3±12.3	66.8±12	*t* test	0.59
Male (%)		16 (64)	38 (58)	χ^2	0.81
NIHSS median score (range)	86	1 (0–11)	2 (0–9)	Mann–Whitney	0.66
Vascular risk factors					
Stroke (%)		1 (4)	11 (17)	Fisher's	0.17
Hypertension (%)		8 (32)	40 (62)	χ^2	0.01
Diabetes (%)		1 (4)	17 (26)	Fisher's	0.02
Imaging parameters					
Onset to assessment, median days (range)		16 (0–43)	9 (0–104)	Mann–Whitney	0.56
Onset to baseline imaging, median days (range)		17 (0–43)	9 (0–104)	Mann–Whitney	0.44
Onset to follow-up imaging, median days (range)		102 (39–1722)	74 (6–1440)	Mann–Whitney	0.03
Lacunar size mm (mean±SD)	74	9.9±3.2	9.7±4.2	*t* test	0.87
Other lacunes baseline		9 (36)	22 (34)	χ^2	0.85
Deep* WML dichotomized 0:1 vs 2:3	80	7 (27)	24 (39)	χ^2	0.85
Periventricular* WML dichotomized 0:1 vs 2:3	80	13 (68)	35 (57)	χ^2	0.39
Anterior† WML dichotomized 0 vs 1:2	10	3 (50)	3 (75)	Fisher's	0.57
Posterior† WML dichotomized 0 vs 1:2	10	1 (17)	2 (50)	Fisher's	0.5
Deep atrophy dichotomized 0:1 vs 2:3		11 (44)	24 (37)	χ^2	0.54
Superficial atrophy dichotomized 0:1 vs 2:3		5 (20)	11 (17)	χ^2	0.74
Basal ganglia EPVS dichotomized 0:2 vs 3:4	80	3 (16)	18 (30)	Fisher's	0.37
Centrum semiovale EPVS dichotomized 0:2 vs 3:4	80	8 (42)	22 (36)	χ^2	0.64

*Fazekas scale; †van Swieten scale.
EPVS indicates enlarged perivascular spaces.

Table 3. Clinical and Imaging Associations of Cavitation in Patients With Definite Cavitation (n=90)

		Definite Cavitation			
	n Where Not 90	Yes n=18	No n=72	Test	*P* Value
Demographics					
Age in years (mean±SD)		69.6±11.1	66.6±12.3	*t* test	0.33
Male (%)		13 (72)	41 (57)	χ^2	0.23
NIHSS median score (range)	86	2 (0–11)	1 (0–9)	Mann–Whitney	0.61
Vascular risk factors					
Stroke (%)		1 (6)	11 (15)	Fisher's	0.45
Hypertension (%)		6 (33)	42 (58)	χ^2	0.056
Diabetes (%)		1 (6)	17 (24)	Fisher's	0.11
Imaging parameters					
Onset to assessment, median days (range)		17 (0–43)	9 (0–104)	Mann–Whitney	0.43
Onset to baseline imaging, median days (range)		18(0–43)	10 (0–104)	Mann–Whitney	0.49
Onset to follow-up imaging, median days (range)		227 (54–1722)	72 (6–1440)	Mann–Whitney	0.0003
Lacunar size mm (mean±SD)	74	9.28±2.82	9.95±4.14	*t* test	0.44
Other lacunes at baseline		6 (33)	25 (35)	χ^2	0.91
Deep* WML dichotomized 0:1 vs 2:3	80	4 (39)	27 (40)		0.76
Periventricular* WML dichotomized 0:1 vs 2:3	80	8 (67)	40 (59)	Fisher's	0.75
Anterior† WML dichotomized 0 vs 1:2	10	3 (50)	3 (75)	Fisher's	0.57
Posterior† WML dichotomized 0 vs 1:2	10	1 (17)	2 (50)	Fisher's	0.5
Deep atrophy dichotomized 0:1 vs 2:3		11 (61)	24 (33)	χ^2	0.03
Superficial atrophy dichotomized 0:1 vs 2:3		5 (28)	11 (15)	χ^2	0.24
Basal ganglia EPVS dichotomized 0:2 vs 3:4	80	3 (25)	3 (25)	18 (26)	1
Centrum semiovale EPVS dichotomized 0:2 vs 3:4	80	5 (42)	25 (37)	χ^2	0.75

*Fazekas scale; †van Swieten scale.
EPVS indicates enlarged perivascular spaces.

other features of small vessel disease) were associated with any evidence of, or definite, cavitation.

In the subgroup of 47 patients with a positive baseline diffusion scan and follow-up MRI, definite cavitation was associated on univariate analysis with increasing time to follow-up (P=0.009) and superficial atrophy (P=0.03). In those with any evidence of cavitation, hypertension was negatively associated with cavitation (P=0.009). No other clinical or imaging features were associated with cavitation in either the whole group or "pure" subgroup.

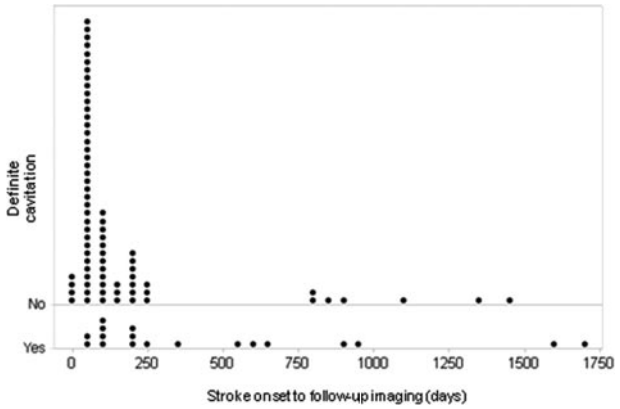

Figure 2. Time to follow-up imaging in patients with and without definite cavitation.

At baseline, 13 of 90 patients (14%) had subcortical spongiform lesions separate from the index acute lacunar infarct (single lesion in 10; 2 lesions in 3). Progression to a definite cavity on follow-up occurred in 2 of these patients, but in neither patient did the index lesion show any evidence of cavitation. From the 11 spongiform lesions that did not progress to a definite cavity, the index lacunar infarct showed progression to a definite cavity in 2 patients.

At baseline, 31 of 90 (34%) patients had concomitant lacunes. Of these 31, 18 (58%) had higher WML scores than the 17 of 59 (29%) without concomitant lacunes at baseline (χ^2 P=0.007); 4 of 31 (4%) patients developed new lacunes between baseline and follow-up imaging (unrelated to the index lesion) over an interval ranging from 76 to 185 days.

Discussion

The proportion of symptomatic lacunar infarcts that undergo cavitation to lacunes is unknown. In this study, one fifth of patients with acute lacunar ischemic stroke showed definite cavitation on follow-up imaging at a median of 227 days (range 54 to 1722) after stroke onset. In a "pure" subgroup (DWI-positive infarct with follow-up MRI), 15% of patients showed definite cavitation. Definite cavitation was associated with increasing time to follow-up in univariate and multivariate analysis, but not with age, NIHSS, lesion size or location, or other features of cerebral small vessel disease, including other lacunes.

The association with increasing time to follow-up remained significant in the "pure" subgroup. If these proportions are similar in other populations, up to four fifths of symptomatic lacunar infarcts may resemble, and be misidentified as, WML at any time up to ≈5 years after stroke, possibly longer.

Definite cavitation was associated with deep atrophy in univariate and multivariate analysis and with superficial atrophy in the "pure" subgroup. Our data indicate that age, stroke severity, and other features of small vessel disease (WML, concomitant lacunes, and enlarged perivascular spaces) were not linked to cavitation. On the other hand, hypertension was negatively associated with cavitation in patients with any evidence of cavitation (in both the whole group and "pure" subgroup) and diabetes in the whole group.

The main strengths of our study are that patients were carefully characterized clinically to be certain of the clinical diagnosis of lacunar stroke, all data were collected according to prespecified criteria, and most patients had baseline MRI, including diffusion. Thus, we can pinpoint precisely when the index lesion started and follow its evolution with precision. The 2 studies from which these data are derived were performed prospectively in the same hospital, using the same data collection, case ascertainment, diagnostic methods, physicians, radiologists, and imaging equipment. We tested associations in the whole, as well as "pure" subgroup and found that they were similar.

Potential limitations were inclusion of a small proportion of patients without a lesion on MRI at baseline; some patients with nonlacunar stroke may have been inadvertently included, despite careful clinical characterization. This may have meant we underestimated the proportion of patients with cavitation. However, after excluding MRI-negative patients, proportions with any evidence of and definite cavitation were similar to the whole group, and to the "pure" subgroup, with overall point estimates ≈15% to 33%.

Minimum time to follow-up imaging was relatively short, but several patients without definite cavitation had follow-up imaging at ≈4 years, and we identified patients with definite cavitation at 54 days. Sample size was relatively small and precluded more complex analyses, so we cannot exclude weak associations between cavitation and imaging-, stroke-, or patient-related features. We were unable to investigate the influence of some factors (eg, duration of symptoms or contrast enhancement) because this information was not collected. Follow-up timing was not fixed, with variable times to follow-up; in the study of lacunar stroke, follow-up was at between one and 3 months, and all patients were recalled for imaging (although not all attended), whereas in the stroke registry, follow-up mostly occurred if the patient developed new symptoms. These selection criteria in the original studies may have influenced cavitation detection rates. Larger studies with fixed follow-up time points are required to obtain more precise data on cavitation.

No previous studies have examined cavitation rates in symptomatic lacunar ischemic stroke, so there is little information with which to draw comparisons. Longitudinal studies show that WML and lacunes increase in number over time, with hypertension (among others) being a risk factor for new lacunes, and diabetes and hypertension being risk factors (among others) for WML progression.[15,16] We found that increased WML severity was associated with concomitant lacunes on baseline imaging, in agreement with previous studies.[17,18] Gouw[15] found that WML progression was modestly correlated with number of new lacunes at follow-up; we were unable to investigate for such a correlation. The apparent coassociation of lacunes and WML suggests that lacunes may represent the extreme end of a spectrum of small vessel changes.

Factors associated with cavitation have been investigated in multiple sclerosis; in longitudinal studies, a ring-enhancing lesion pattern is associated with cavity development,[19–22] but predictive power is limited because of variability in cavity development, with some evidence that cavitation is patient-specific. Differences in multiple sclerosis lesion evolution in the same patient have also been demonstrated, suggesting local inflammatory reaction or location may be more relevant than individual susceptibility in leading to permanent axonal loss.[23] Duration of symptoms may influence whether cavitation occurs (we did not record this), although we found no association with NIHSS, another marker of stroke severity. In animals, duration of middle cerebral artery occlusion has been shown to influence infarct cavitation.[24]

The molecular processes underlying cerebral tissue damage and repair, through the stages of tissue infarction and "rarefaction," leading to gliosis and cavitation, are complex, and as yet incompletely identified.[25] Histologically, a phase of chronic inflammation, including cavitation, was identified from 10 days to 53 years in patients with cortical and lacunar infarction.[26] In our study, the earliest time at which a lesion demonstrated any evidence of cavitation was 39 days, and 54 days for definite cavitation. Matrix metalloproteinases are important factors for tissue remodeling implicated in all main cerebrovascular diseases including ischemia and WML in vascular dementia.[27,28] Higher levels of matrix metalloproteinase-9 may be related to neurological deterioration in the first 7 days after acute lacunar infarction, but there is no information on whether high matrix metalloproteinase levels are associated with cavitation.[29]

Thirteen patients in our study had spongiform lesions (possible cavities) separate from the index lesion at baseline; in 2 patients, these progressed to definite cavities, but the index lesion showed no cavitation. Similarly, 2 patients with definite cavitation of the index lesion showed no progression to cavitation in nonindex spongiform lesions. Cavitation may therefore occur on a "per lesion" rather than "per patient" basis.

What are the implications if only one of 5 acute symptomatic lacunar infarcts becomes a cavity and the other 4 continue to resemble WML? In epidemiology (including risk factor) and pathophysiology studies of lacunar infarction, which only count lacunes as old lacunar infarcts, the true burden of lacunar disease may be underestimated by as much as 5 times. With the difficulties in distinguishing between WML and noncavitated lacunar infarction, consideration should be given to abandoning the term WML in favor of a term such as small vessel changes, correlating acute lacunar infarcts, WML, and lacunes with symptoms wherever possible. Our findings should be confirmed in larger prospective studies of acute lacunar stroke, with follow-up at prespecified time intervals.

Summary

Lacunes are often counted in epidemiological studies as old lacunar infarcts, but we found definite cavitation of symptomatic lacunar infarcts occurring in only one fifth of patients; most lacunar infarcts may continue to resemble WML. The true burden of lacunar stroke disease on imaging may thus be substantially underestimated in studies that only count lacunes. We found that cavitation was associated with increasing time to follow-up imaging and deep cerebral atrophy. Larger prospective studies, with prespecified follow-up intervals, are required.

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Disclosures

None.

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Wide Variation in Definition, Detection, and Description of Lacunar Lesions on Imaging

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Background and Purpose—Variation in the definition of lacunar lesions on imaging and difficulties in their detection may be hampering lacunar stroke research. We assessed literature definitions of imaging lacunar lesions and the definitions and detection of lacunar lesions among small-vessel disease researchers.

Methods—We assessed definitions of imaging lacunar lesion in 50 randomly selected articles from 3 stroke-related journals and an online survey of small-vessel disease researchers. In the literature review, we assessed clinical/imaging definitions of lacunar stroke. In the survey, we assessed lacunar lesion detection, effects of lesion appearance, background white matter lesions, and provision of relevant data.

Results—Among 50 articles, imaging definitions were varied and often limited; size was stated in 21 of 43 (49%) studies of acute and in 9 of 20 (45%) studies of old lesions and site in 18 (42%) and 4 (20%), respectively. Clinical definitions also varied, and images were read mostly by nonradiologists. Among 56 survey respondents, multiple descriptions were used for recent and old, symptomatic and asymptomatic, lesions on imaging. Most agreed on definitions for site (98%) and "old lacunar infarct" (61%) size. Cavitated (vs noncavitated) lesions were usually identified as lacunar lesions; with increasing white matter lesions, however, noncavitated lesions were very unlikely to be identified, even with prior imaging available (7.8%).

Conclusions—Imaging definitions of lacunar lesions vary widely, in part due to variation in lesion detection and classification. A consensus for imaging definitions of small-vessel disease features would be helpful. **(*Stroke*. 2011;42:00-00.)**

Key Words: acute stroke ■ acute stroke syndromes ■ acute cerebral infarction ■ brain infarction ■ lacunar infarcts ■ cerebral lacunes ■ white matter disease ■ leukoaraiosis ■ diagnostic methods ■ other diagnostic testing ■ computed tomography ■ magnetic resonance imaging

Lacunar stroke accounts for ≈25% of ischemic stroke.[1] The lacunar hypothesis implies that classic lacunar syndromes are caused by small, deep brain infarcts, secondary to occlusion of a single penetrating artery.[2] However, no clinical stroke syndrome is absolutely specific with respect to pathophysiology. The clinical value of the lacunar hypothesis has been questioned by some, because as many as 20% of lacunar strokes may be caused by pathologies other than a small, deep infarct, including hemorrhage and cortical infarction.[3,4] Lacunar infarcts are often defined in stroke registries by a combination of clinical features (with or without inclusion of risk factors) and imaging findings,[5] and controversy exists as to whether emboli are an important cause of lacunar infarction.[6–8]

On brain imaging, lacunar lesions form part of a spectrum of features of cerebral small-vessel disease (SVD), which often have overlapping appearances. Some symptomatic lacunar infarcts may never cavitate.[9] Several radiologic terms used for lacunar lesions (for example, "lacunar infarct," "lacunar stroke," and "lacune") appear to be used interchangeably,[10] which may be contributing to the current debate on the causes of lacunar stroke.[6–8]

A survey of 13 neuropathology laboratories showed wide variation in the definitions of SVD features.[11] Variations in clinical, neuropathologic, and radiologic terminology and definitions have complicated research in other related areas such as vascular dementia.[11–17] Ways of reducing heterogeneity by providing standardized classification systems for the imaging assessment of other radiologic features of SVD (white matter lesions [WMLs][18] and brain microbleeds[19]) have been addressed but not the consistency of imaging assessment in lacunar stroke.

In this study, we surveyed the literature to quantify the range and variation of imaging definitions of lacunar lesions and related methodology, including clinical definitions, and used an online survey to assess how current SVD researchers detect and describe lacunar lesions.

Methods

Literature Review

We searched PubMed for articles published between 1998 and 2008 in 3 journals with a focus on stroke (*Stroke*, *Cerebrovascular Diseases*, and the *Journal of Neurology*) by using the terms "lacu-

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Table 1. Terms Used for Acute (n=43) and Old (n=20) Lacunar Lesions on Imaging in the Literature

Acute Lacunar Lesions (n=43)	n (%)	Old Lacunar Lesions (n=20)	n (%)
"Infarct"/"lesion"		No reference to age	
Lacunar infarct/lesion	22 (51.2)	Lacunar infarct/lesion	8 (40)
Subcortical infarct/lesion	6 (14)	Lacunar stroke	1 (5)
Subcortical MCA territory infarct	1 (2.3)	Subcortical lesion	1 (5)
Deep subcortical infarct	1 (2.3)	Deep infarct	1 (5)
Small, deep lesion	2 (4.7)	Small infarct	1 (5)
Deep brain/focal infarct	2 (4.7)	Reference to age	
Hypodense lesion*	1 (2.3)	Old lacunar infarct	1 (5)
Striatocapsular infarct	1 (2.3)	Chronic subcortical infarct	1 (5)
Lesion	1 (2.3)	Reference to symptoms	
"Stroke"		Silent lacunar infarct	4 (20)
Subcortical stroke	1 (2.3)	Nonspecific/no reference to lesion	
Deep ischemic stroke	1 (2.3)	Lesion	1 (5)
Nonspecific/no reference to lesion		No reference to lesion	1 (5)
Focal hyperintensity on DWI	1 (2.3)		
No reference to lesion	1 (2.3)		

MCA indicates middle cerebral artery; DWI, diffusion-weighted imaging.
*On CT and MRI.

nar," "lacune," and "subcortical." We tested the data collection form on 10 articles before assessing another 50 articles describing lacunar stroke studies in humans. Articles were selected at random by using a random-number generator. Data were extracted by 2 observers (G.M.P., F.J.M.), with data cross-checked by G.M.P., and the third author arbitrated any disagreements. When there were ≥2 articles by the same authors, we took care to avoid data duplication.

We collected data on corresponding author discipline and inclusion of a radiologist in the authorship. We collected details about terminology, definitions, lesion descriptors, imaging modality, timing of imaging, description of magnetic resonance imaging (MRI) sequences, and clinical definitions, including the stroke classification system used and whether imaging findings were incorporated into the clinical definition. For old lacunar lesions only, we assessed differentiation from enlarged perivascular spaces (EPVSs) and correlation with prior relevant symptoms. We also collected data about discipline, number, blinding, and experience of readers.

Literature Review Analysis

We assessed the proportion of articles providing clinical and imaging definitions, imaging modality used, corresponding author discipline, and the number with a radiologist in the authorship. We listed all terms used to describe lacunar lesions on imaging and the proportion using each. We determined proportions (1) describing lesion size, site, attenuation/intensity, and clinical terminology; (2) providing details about the timing of imaging; (3) attempting to correlate old lesions with symptoms; and (4) attempting to differentiate old lesions from EPVSs.

Online Survey

We established an online survey (SurveyMonkey) to send to researchers with an interest in cerebral SVD. We asked questions about participant discipline, previous publication on lacunar stroke, and involvement of a radiologist in image interpretation.

To assess definitions, we asked participants to select a single answer from a list of several options for site and size of lacunar lesions and definition of EPVSs. To assess detection and description of lacunar lesions, we used 10 case-based examples on brain computed tomography (CT) and MRI. MRI sequences included axial T2, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). We provided a size marker/description of size in each case. We included a "comments box" for all questions. We tested the effects of lesion appearance, presence of concomitant WMLs, and provision of prior imaging on lesion detection. We chose images that allowed us to test 1 or several of these features and included varying amounts of relevant prior information. For case-based examples of old lacunar lesions, we showed T2 and FLAIR sequences (while withholding the positive baseline DWI), provided a history of baseline symptoms in the relevant hemisphere, and indicated that no hemorrhage was visible on MRI gradient-echo imaging. To assess the degree of certainty in lesion detection, we asked participants to indicate whether they thought the lesion was present: "yes, definitely"; "yes, probably"; "yes, possibly"; or "no." We identified SVD researchers from our literature review and from prior knowledge among our stroke research group (for example, previous collaboration). We tested the survey initially in our stroke research group. A survey web link was sent to 147 SVD researchers. We indicated that the survey would take ≈10 to 15 minutes to complete and that responses were anonymous. We allowed 3 weeks for completion and sent 2 reminders, extending the deadline by a further 2 weeks each time. We also encouraged sending of the survey link to other interested colleagues.

Survey Analysis

We assessed the number of participants completing each question, their discipline, and previous publication on lacunar stroke (including involvement of a radiologist). For definitions of lacunar lesions and EPVSs, we assessed the number of participants selecting each of the definitions provided. In the case-based examples, we assessed the effects of lesion appearances, concomitant WMLs, provision of prior imaging on lacunar lesion detection/description, and differentiation of lacunes from EPVSs.

Results

Literature Review

Article Type, Authorship, and Type of Lesion

From a total of 362 articles, we randomly selected 50 articles (22 from *Stroke*, 13 from the *Journal of Neurology*, and 15 from *Cerebrovascular Diseases*), consisting of 47 original articles and 3 case reports. The corresponding author was usually a neurologist (34 of 50, 68%). The authorship included a radiologist in 13 (26%) articles: 8 of 13 (62%) were general radiologists and 5 (28%) were neuroradiologists (that is, a neuroradiologist con-

Table 2. Descriptions of Site and Size for Acute (n=43) and Old (n=20) Lacunar Lesions in the Literature

Acute lacunar lesions, site defined, n (%)	18 (42)
General description where site defined	
Areas supplied by deep perforants	7 (38.9)
Subcortical MCA territory	1 (5.56)
Specific territories where site defined	
Supratentorial white matter	1 (5.56)
IC, thalamus, BG, CR, pons, and CS	1 (5.56)
Lentiform nucleus	1 (5.56)
Thalamus, capsule, protuberance, and mesencephalon	1 (5.56)
Subcortical, ie, CR, IC, and BG	1 (5.56)
CR, BG, thalamus, and caudate nucleus	1 (5.56)
IC, CR, CS, CN, P, GP, thalamus, midbrain, pons, and medulla	1 (5.56)
Old lacunar lesions, site defined, n (%)	4 (20)
Territory supplied by deep/superficial small perforating arteries	1 (25)
Deep in the brain	1 (25)
Frontal, parieto-occipital, temporal, BG, and infratentorial regions*	1 (25)
IC, thalamus, BG, CR, pons, and CS	1 (25)
Acute lacunar lesions, size defined, n (%)	21 (49)
Minimum size stated†	4 (9)
Maximum size stated‡	19 (44)
Old lacunar lesions, size defined, n (%)	9 (45)
Minimum size stated†	6 (30)
Maximum size stated‡	8 (40)

MCA indicates middle cerebral artery; IC, internal capsule; BG, basal ganglia; CR, corona radiata; CS, centum semiovale; CN, caudate nucleus; P, putamen; and GP, globus pallidus.

*As used for white matter hyperintensities.

†For acute lesions, range, 3–5 mm; old lesions, range, 10–20 mm.

‡For acute lesions, values of 2, 3, or 5 mm; old lesions, range, 10–20 mm.

Table 3. Terminology and Descriptions Used for Clinical Lacunar Stroke (n=38) and Clinical Definitions Used for Lacunar Stroke (n=25) in the Literature

Terminology and descriptions used for clinical lacunar stroke (n=38)	n (%)
Lacunar stroke/syndrome/infarction	28 (75.7)
Lacunar, large-vessel cervical, or intracranial atherosclerosis	1 (2.7)
Ischemic stroke	2 (5.4)
Subcortical MCA territory infarction/lacunar syndrome	1 (2.7)
Subcortical stroke/lesion/infarction	3 (8.1)
Acute focal symptoms, eg, hemiparesis or acute aphasia, diagnosed according to ICD-9	1 (2.7)
Pure sensory stroke	1 (2.7)
Cerebrovascular attack	1 (2.7)
Clinical definitions used for lacunar stroke (n=25) in the literature	
Lacunar syndrome (with or without description of each of the 5 classic syndromes)	14 (56)
Lacunar syndrome with reference to imaging findings	5 (20)
Symptoms specific to condition under investigation	1 (4)
Nonspecific	
Acute focal deficit confirmed by an associated lesion on CT or MRI	1 (4)
Focal neurologic symptoms	1 (4)
Minor focal cerebrovascular events	1 (4)
Ischemic stroke	1 (4)
Syndrome associated with lacunar infarction in the deep white matter or brain stem	1 (4)

MCA indicates middle cerebral artery; ICD, International Classification of Diseases.

tributed to 10% of articles overall). Thirty (60%) studies concerned acute lacunar lesions and 7 (14%), old lacunar lesions; 13 (26%) studies concerned both. Thus, a total of 43 articles were relevant for definitions of acute lacunar lesions and 20, of old lacunar lesions.

Radiologic Terminology and Definitions for Lacunar Lesions

Thirteen different terms were used for acute and 10 for old lacunar lesions (Table 1). "Lacunar infarct" and "lacunar stroke" were used for both acute and old lesions. An imaging definition was provided in 26 of 43 (60%) articles describing acute and in 8 of 20 (40%) articles describing old lesions. Among these, 13 articles concerned both acute and old lesions, and most (6 of 13, 46%) failed to provide a definition for either type of lesion: 4 (31%) provided a definition for only 1 lesion type, 1 (8%) used the same definition for both, and only 2 (15%) provided a separate definition for each.

Radiologic Descriptors for Lacunar Lesions: Site and Size

Lacunar lesion site was defined in 18 of 43 (42%) studies of acute and in 4 of 20 (20%) studies of old lesions, with marked variation in descriptions (Table 2). Size was provided in 21 of 43 (49%) and in 9 of 20 (45%) studies, respectively, with a greater maximum size used for acute (25 mm) versus old (20 mm) lesions (Table 2).

EPVSs and Their Differentiation From Lacunes

Of studies on old lacunar lesions, most (17 of 20, 85%) articles did not distinguish EPVSs from old lacunar lesions. A description of EPVSs was given in 7 of 50 (14%) articles on acute lesions, with 7 different descriptions given.

Clinical Terminology, Definitions, and Descriptions

Thirty-eight (76%) articles specified the clinical terminology used (Table 3). A clinical stroke classification system was used in 8 of 50 (16%) articles (6 using a risk factor–based system,[20] 1 a risk factor–free system,[1] and 1 a combination of systems). A clinical stroke definition was provided in 25 of 50 (50%) articles, with most (19 of 25, 76%) referring to a "classic lacunar syndrome," either with or without reference to associated imaging findings (Table 3). From 20 articles concerning old lesions, correlation with possible, relevant, previous stroke symptoms was attempted in only 2 (10%) cases.

Imaging Modality and MRI Sequences

Among 43 studies concerning acute lesions, 22 (51%) used MRI and 7 (16%) used CT. DWI was performed in 33%. Most (31, 72%) did not provide any details on the timing of imaging in relation to the onset of stroke symptoms. For old

Table 4. Definitions of Lacunar Lesions and EPVSs (Single Answer Allowed, n=44, Except Where Indicated) in the Online Survey of Current SVD Researchers

"What do you consider the best definition of size for the following lacunar lesions?"	3–15 mm	3–20 mm	3–25 mm	Unsure
Acute lacunar infarct, n (%)	13 (29.5)	17 (38.6)	9 (20.5)	4 (9.1)
Old lacunar infarct, n (%)	27 (61.4)	12 (27.3)	1 (2.3)	3 (6.8)
Lacune, n (%)*	24 (55.8)	9 (20.9)	1 (2.3)	7 (16.3)
"What do you consider the best definition regarding site of lacunar lesions?"	n (%)			
Territory of deep perforating arteries—brain stem, basal ganglia (caudate nucleus, lentiform nucleus, internal capsule, thalamus), and white matter (corona radiata, centrum semiovale)	43 (97.7)			
Subcortical MCA territory	0 (0)			
Clinically relevant areas	0 (0)			
Deep white matter of brain and/or brain stem	1 (2.3)			
Deep in the brain	0 (0)			
"What do you consider the best definition of enlarged perivascular (Virchow-Robin) spaces?"	n (%)			
≤2 mm, round or linear lesions along the course of penetrating arteries with intensity close to CSF	7 (15.9)			
≤2 mm, round or linear lesions at point of entry of MCA lenticulostriate arteries into basal ganglia, with intensity close to CSF	4 (9.1)			
Small, round or linear lesions along the course of penetrating arteries, with intensity close to CSF	27 (61.4)			
Small, round or linear lesions at point of entry of MCA lenticulostriate arteries into basal ganglia, with intensity close to CSF	5 (11.4)			
Uncertain	1 (2.3)			

MCA indicates middle cerebral artery; CSF, cerebrospinal fluid.
*n=43.

lesions, MRI was used in 15 of 20 (75%) articles, CT in 4 (20%), and both modalities in 1 (5%). MRI sequences used to diagnose lacunar lesions were described in 11 (31%) studies concerning acute and in 7 (44%) studies concerning old lacunar lesions. Most articles did not provide a description of lesion attenuation or signal intensity.

Discipline, Number, and Blinding of Image Readers

Among the 20 of 50 (40%) articles providing details on who interpreted brain imaging, most (13 of 20, 65%) indicated that imaging was interpreted by nonradiologists (including at least 1 neurologist in 12 articles and a neuropathologist in 1). Overall, 17 of 50 (34%) studies provided information on blinding of readers, 6 of 50 (12%) indicated the level of reader experience, and 23 of 50 (46%) reported the number of readers.

Online Survey of SVD Researchers

Of 147 researchers with an interest in cerebral SVD to whom the online survey was sent, 56 responded to the survey: 46 of 56 (82%) completed all 10 case-based questions and 44 of 56 (79%) completed the entire survey. The majority of participants were neurologists (25 of 44, 57%). Other disciplines were stroke physicians (12 of 44, 27%), neuroradiologists (6 of 44, 14%), and a geriatrician (1 of 44, 2%). Most respondents (37 of 44, 84.1%) had published articles on SVD, most with involvement of a radiologist (27 of 37, 73%).

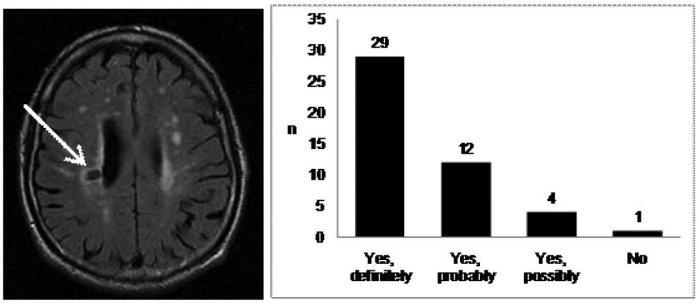
Radiologic Definitions of Lacunar Lesions and EPVSs

For definitions of lacunar lesion site, most (43 of 44, 97.7%) respondents selected "territory of deep perforating arteries–brain stem, basal ganglia and white matter" (Table 4). Definitions selected for size of acute and old lacunar lesions were more varied: for "acute lacunar infarct," 17 of 44 (38.6%) selected 3 to 20 mm, and 9 of 44 (20.5%) selected 3 to 25 mm (Table 4); for "old lacunar infarct," 27 (61.4%) selected 3 to 15 mm and 1 participant selected 3 to 25 mm. Numbers of participants selecting each size category (3 to 15 mm, 3 to 20 mm, or 3 to 25 mm) were similar for both "old lacunar infarct" and "lacune." For the EPVSs definition, most (27 of 44, 61.4%) selected "small, round, or linear lesions along the course of penetrating arteries with intensity close to CSF" (Table 4). Definitions we provided that did not include specific size criteria were selected more often than those that did (32 of 44, 72.7%, vs 11 of 44, 25%, respectively). Heterogeneity in descriptions for site, size, and presence of cavitation existed between each group of clinicians, including neuroradiologists.

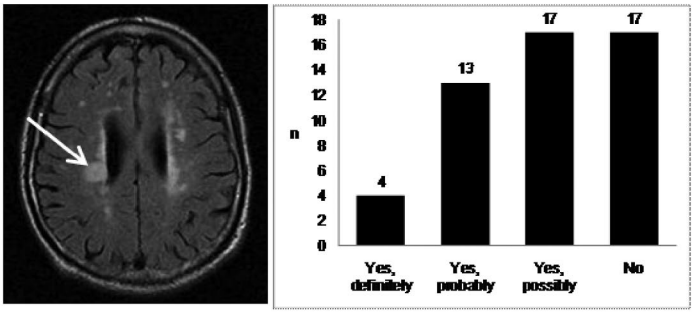
Old Lacunar Lesion Detection/Description: Effect of Lesion Appearance, WMLs, and Prior Imaging

There was a strong tendency to identify cerebrospinal fluid–containing cavities as lacunar infarcts. Thus, cavitated lesions were identified as lacunar stroke lesions with certainty by 29 of 46 (63%) participants (Figure 1A). In the presence of concomitant WMLs, cavitated lesions were much more likely to be identified as lacunar stroke lesions than were noncavitated lesions (29 of 46, 63%, vs 4 of 51, 7.8%, respectively; Figure 1, A and B; χ^2 $P<0.001$), even when baseline FLAIR images were provided (Figure 1C). Indeed, when shown a CT scan with a cavity of cerebrospinal fluid density in the thalamus (without information on whether the original pres-

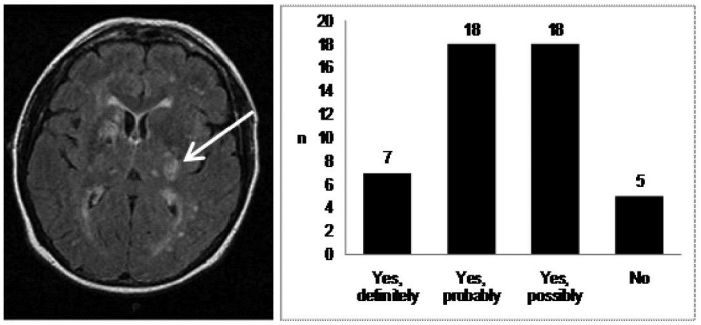
A Cavitated lesion with WML ("Is there a lesion in the right hemisphere consistent with a lacunar infarct 18 months previously?; n=46)



B Non-cavitated lesion with WML ("Is there a lesion in the right hemisphere consistent with a lacunar infarct 2 years previously?"; n=51)



C Non-cavitated lesion with WML, but provision of baseline FLAIR imaging in survey ("Is there a lesion in the left cerebral hemisphere consistent with a lacunar infarct?; n=48)



D Non-cavitated but large lesion, with no WML ("Is there a lesion in the right hemisphere consistent with a lacunar infarct 18 months previously?; n=50)

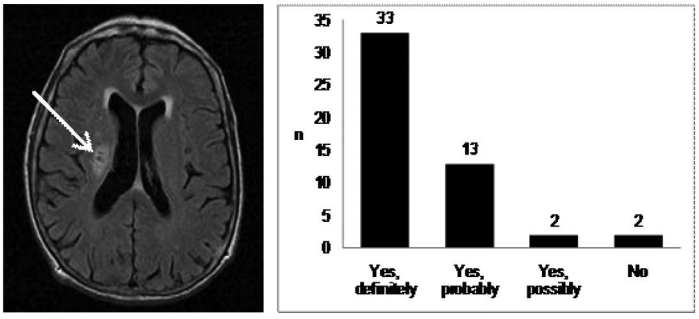


Figure 1. Effect of cavitation and WMLs on level/certainty of detection of old lacunar stroke lesions.

enting lesion was a hemorrhage or infarct), most respondents selected "lacunar infarct" (25 of 56, 44.6%; Figure 2). Noncavitated lesions were identified as lacunar stroke lesions only when they were large and in the absence of other WMLs (33 of 50, 66%, Figure 1D).

Radiologic Differentiation Between Lacunes and EPVSs

Prominent EPVSs were frequently mistaken for lacunar infarcts (for example, 21 of 47, 44.7%, selecting ">5 lacunes" when shown the example in Figure 3).

"Please indicate which term you consider most appropriate for the lesion circled in the right thalamus" (n=56)

	n (%)
Lacunar infarct	25 (44.6)
Lacunar stroke	3 (5.4)
Subcortical infarct	3 (5.4)
Subcortical stroke	0 (0)
Small, deep infarct	4 (7.1)
Small, deep stroke	3 (5.4)
Lacune	14 (25)
Black hole	3 (5.4)
White matter lesion	1 (1.8)
Other	0 (0)

Figure 2. Effect of lesion appearance on lacunar lesion description.

Radiologic Terminology: Effect of Lesion Site

Lacunar lesion descriptions varied depending on site, being greatest for a lesion in the brain stem. From a list of multiple terms provided, 20 of 56 (35.7%) opted to provide an alternative description for the brainstem lesion, many of which implied an underlying mechanism (Figure 4).

Discussion

In a sample of 50 articles from the lacunar stroke literature and in an online survey of cerebral SVD researchers, there was marked variation in imaging terminology and descriptions for lacunar lesions. In the literature review, any type of imaging definition was provided in 26 (60%) studies of acute and in 8 (40%) of old lacunar lesions, with the terms "lacunar infarct" and "lacunar stroke" used for both acute and old, symptomatic and asymptomatic, lesions. Few articles attempted to differentiate old, cavitated lacunes from EPVSs or to seek relevant previous symptoms. Clinical terminology also varied widely and was provided in only 50% of studies. Most articles used a risk factor–based clinical stroke classification system, and the minority indicated a definition for lacunar stroke that incorporated both clinical and imaging information. For acute lesions, only a third of those using MRI used DWI. Nonradiologists interpreted images in most cases. Most studies did not describe lesion attenuation/signal intensity or the diagnostic sequences used. In the online survey, most agreed on definitions for lacunar lesion site and EPVS, but there was less agreement for lacunar lesion size. There was wide variation in lesion recognition and classification: cavitated lesions of any size were detected with the highest degree of confidence but were described by multiple terms, including "lacunar infarct" and "lacunar stroke" (without information about a possible previous hemorrhage or relevant symptoms). Detection of noncavitated lacunar infarcts in the presence of WMLs was poor, and differentiation of lacunes from EPVSs was poor.

The strengths of our study include assessment of multiple aspects of definitions and terminology for both acute and old lacunar lesions, both in the literature and among interested experts. For the literature review, we selected articles at random from 3 journals with a stroke focus, which are likely to be reasonably representative of articles in the stroke literature. We collected data on clinical and imaging-related data, thus enabling a wider overall impression of potential problems in lacunar stroke research. We designed a structured online survey to assess multiple aspects of lacunar lesion description and detection. We tested the survey among local stroke researchers to improve the design and relevance before its distribution. Images were carefully chosen to allow us to test specific features that might influence lacunar lesion detection and description. By specifically identifying researchers with an interest in cerebral SVD, we gathered opinions that are likely to be most relevant to lacunar stroke research.

There are limitations of our study. For the literature review, we randomly selected 50 articles from a total of 362 articles

"How many lacunes are visible?" (T2 images shown in online version)

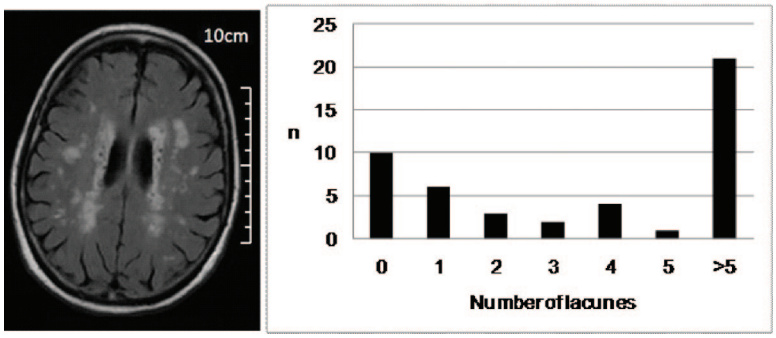
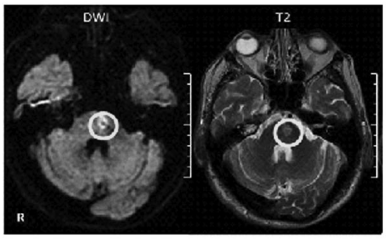


Figure 3. Differentiation of lacunes from EPVSs (data shown for 47 respondents).

"Which term you consider most appropriate for this acute lesion in a patient with a 17-hour history of left pontine lacunar stroke symptoms?" (n=56; FLAIR sequence not shown)



	n (%)
Lacunar infarct	23 (41.1)
Lacunar stroke	1 (1.8)
Subcortical infarct	1 (1.8)
Subcortical stroke	1 (1.8)
Small, deep infarct	9 (16.1)
Small, deep stroke	0 (0)
Lacune	0 (0)
Black hole	1 (1.8)
White matter lesion	0 (0)
Other*	20 (35.7)

*Other
Pontine infarct (n=6)
Probable infarct - lacune
Branch artery infarct
Branch artery disease
Pontine paramedian infarct (n=3)
Pontine branch infarct
Hyperintense vascular lesion in brainstem
Ischemic lacunar stroke
Pontine perforator stroke
Left pontine ischemic lesion
Brain or pontine infarction in paramedian territory, not lacunar
Lacunar stroke due to proximal perforator occlusion, suggesting large artery disease/embolism as the cause
Probably progressive subacute pontine infarct

Figure 4. Effect of lacunar lesion site on descriptions used.

in a PubMed search of 3 stroke-related journals; therefore, our data represent a small sample of the lacunar stroke literature. We had planned to sample a larger proportion, but there seemed little point when the first 50 articles yielded so much variation in imaging/clinical definitions of lacunar lesions and related methodologies. Although we did not test other journals, it is unlikely that articles in nonstroke-focused journals would show any less variation. In the online survey, only a third of those invited to participate took part, and a minority were neuroradiologists; however, neurologists have contributed the highest proportion of the lacunar stroke literature. The reasons for nonparticipation and any differences between participants/nonparticipants are unknown, as the responses were anonymous. Forty-four people completed the entire survey, so our data represent only a fraction of opinions; however, most were interested in SVD, therefore, we believe that the responses were sufficient in both detail and quality to document a lack of harmony in imaging assessment of lacunar lesions, even among interested experts who would be more likely to communicate frequently with each other at meetings and through the literature. In most cases, we allowed only a single answer, but participants were able to add further comments by using a "comments box."

As in a previous study of neuropathology laboratories,[11] we found marked variation in lacunar lesion definitions. In the survey, we found marked variation for brainstem lesions and a tendency to imply causation, rather than simply to describe the imaging appearance. In both the literature and the online survey, we found interchangeable use of terminology for acute and old, symptomatic and asymptomatic, lacunar lesions, implying a similar etiology, even though etiology may be heterogeneous.[10] Identification of old lacunar lesions was best for cavitated lesions, but because only a fifth of symptomatic lacunar infarcts cavitate, cavitation is an unreliable marker for prior lacunar infarction.[9]

Variation in imaging definitions and heterogeneity in the reporting of other lacunar stroke-related features may be contributing to ongoing controversies in lacunar stroke research,[6–8,21–25] for example, bias in clinical classification systems[20,26]; misclassification of cortical as lacunar stroke, based on clinical symptoms alone[3,4]; suboptimal detection of acute lacunar infarcts; difficulties in differentiating old lacunes from EPVSs; and limited information on previous neurologic symptoms.

Many SVD researchers do not have access to neuroradiology expertise. It is important that radiologic assessment of lacunar lesions is performed by those with at least some experience, training, and interest in the field. A standardized approach to imaging definitions of lacunar lesions is essential to improve the understanding of lacunar stroke and SVD. This may be best achieved by aiming for a consensus among interested experts, both radiologists and clinicians, with examples and perhaps a validated test set of images, which could be used for training. The imaging definition of lacunar lesions on brain imaging should include an accurate description of the size, shape, location, and appearance in terms of CT attenuation or MRI signal intensity (on all appropriate MRI sequences, but particularly T2, FLAIR, T2*, and DWI). Recent or prior lacunar hemorrhage, which causes ≈5% of true lacunar strokes,[27,28] should be identified by T2* or susceptibility-weighted sequences as a routine. Observers should describe what they see, not what they think they see,

as any assumed etiology may be erroneous and further complicate efforts to improve understanding of the true underlying cause in cerebral SVD. The imaging definition should be considered in conjunction with clinical information about the acute stroke and any prior stroke or underlying neurologic impairment.

In our center, we define a recent lacunar "infarct" (as distinct from a hemorrhage) on MRI as a "round or ovoid lesion of increased signal relative to white or deep gray matter on DWI, FLAIR, or T2; hypointense on the apparent diffusion coefficient map (or decreased attenuation relative to white/gray matter on CT) measuring ≤20 mm in maximal diameter, in the cerebral hemispheric white matter or basal ganglia or in the brain stem." In concurrence with some, but by no means all, SVD researchers, we consider 20 mm, rather than 15 mm, the upper limit for acute lacunar infarcts. Lacunar lesions may or may not cavitate with time to form "lacunes."[9] We use the term "lacune" to mean cerebrospinal fluid signal/attenuation-containing cavities that are round or ovoid lesions, measuring 3 to 20 mm in the cerebral hemispheric white matter, basal ganglia, or brain stem. We try to correlate both acute lacunar lesions and old lacunes/noncavitated lacunar lesions with recent or previous stroke symptoms and signs, respectively. Because many acute lacunar lesions will decrease in size over time, we are cautious about calling cavities >1.5-cm diameter "lacunes" unless there is no other explanation. We define clinical lacunar syndromes according to the Oxfordshire Community Stroke Project Classification, a risk factor–free definition based on neurologic symptoms and signs only.[1]

Other research groups must have other definitions, as with ours, possibly arising from particular circumstances of their own practice, such as available technologies, interests, expertise, and beliefs about likely causes of lacunar stroke. However it is achieved, a consensus in lacunar lesion definition, with agreement on use of terminology and then more consistent and accurate use of the terms, accurate lesion description, correlation with relevant clinical symptoms/prior hemorrhage wherever possible, an attempt to distinguish between old lacunes and EPVSs, and avoidance of assumptions about etiology, is urgently needed.

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Disclosures

None.

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Cerebral small-vessel disease

What lies beyond the early years?

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The term cerebral small-vessel disease (SVD) encompasses a range of features visible on brain imaging, including lacunar infarction (from the Latin *lacunae*, a tiny hole, pit, or cavity), leukoaraiosis (from the Greek *leuko*, white, and *araiosis*, rarefaction), enlarged perivascular spaces (producing an appearance of *état criblé*, or cribriform state, from the Latin *cribriform*, perforated), and brain microbleeds. The investigative approach to cerebral SVD—including lacunar stroke—has been revolutionized in the last 4 decades by the advent of CT and MRI, which have overcome many of the limitations imposed by the old pathology-centered approach,[1] whereby low early case-fatality rates necessitated most pathologic material being examined long after clinical symptoms had occurred. MRI in particular has markedly improved our ability to detect cerebral SVD in vivo, enabling detection of microangiopathic changes such as enlarged perivascular spaces and microbleeds, although there is marked variation in imaging terminology and descriptions for lacunar lesions.[2]

Until recently, there has been relative neglect of small-vessel lacunar stroke—once considered the most benign ischemic stroke subtype—with attention having been mainly focused on large-artery cortical ischemic stroke, a trend reflected in the advances made in therapeutic options for stroke. The prognosis during the first few years for small-vessel stroke is more favorable (in terms of survival and disability) than large-vessel ischemic stroke; but in the long term, there is a greater risk of death, stroke recurrence, cognitive dysfunction, and dementia than previously realized,[3] and a similar loss of quality-adjusted life expectancy compared to large-artery stroke. Similarly, leukoaraiosis, once considered a neutral term, is now known to be a marker of poor prognosis, particularly in terms of increased mortality and risk of dementia.[4] The prognostic significance of newer markers of cerebral SVD, namely enlarged perivascular spaces and brain microbleeds, have yet to be fully established.

In this issue of *Neurology*®, Melkas et al.[5] show that in a well-characterized ischemic stroke cohort with ultra-long (12-year) follow-up, acute index stroke attributable to cerebral SVD was associated with poorer long-term survival and higher risk of cardiac death than other stroke subtypes. Limitations imposed by the authors' use of a risk-factor–based stroke classification system and selection bias from inclusion of only hospitalized patients with SVD may account for differences in findings compared to another recent study comparing vascular outcomes between ischemic stroke subtypes,[6] and should be considered in future confirmatory studies.

Despite its importance, data from clinically eloquent lacunar strokes offer a skewed view and probably minimize the true extent of the problem, particularly in regards to the cognitive damage produced by these lesions in the elderly. Silent lacunar strokes occur in as many as one-third of people over the age of 65, and more than double the risk for development of dementia, particularly when present in the thalamus.[7] The clinical manifestations of most silent lacunes include problems of cognition, mood, and behavior that may fall in a blind spot of clinical neurologists.[8] These small-vessel lesions affect particularly executive function, attention, and speed of processing and probably sever central cholinergic pathways.[9] Despite a focus on the causes and associations of cerebral SVD in recent years, the exact mechanisms underlying lacunar stroke, and cerebral SVD, remain unclear, with proposed mechanisms including lipohyalinosis, arteriosclerosis, poor cerebral blood flow, vasospasm, and abnormal endothelial function.[10] Other potentially important factors not usually considered include hyperhomocysteinemia, low values of vitamin B12,[11] and obstructive sleep apnea.[12] Acute treatment and secondary prevention of ischemic stroke is therefore currently similar across all stroke subtypes; current therapeutic options are likely to remain limited until further progress is made in understanding the pathophysiologic pro-

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cesses underlying cerebral SVD. The recent acceleration in studies aiming to elucidate the true etiology of cerebral SVD, including the utilization of newer imaging techniques for detecting and following microangiopathic markers, is extremely promising and highlights the increasingly urgent search for a potential therapeutic target for this disabling and life-threatening disease.

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Title

Cerebral Microbleeds: Pathophysiology to Clinical Practice

Chapter 5: Microbleed mimics

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Introduction

An awareness of the abnormalities that mimic microbleeds on gradient-recalled echo (GRE) magnetic resonance imaging (MRI) is essential to investigations of their prognostic and therapeutic significance, as well as future implementation of the results of these investigations in clinical practice. These 'microbleed mimics' have similar morphologies and signal properties to microbleeds on T1- & T2-weighted spin echo and GRE MRI sequences.(1) The keys to the identification of microbleed mimics are an awareness of their distinctive imaging hallmarks and the use of other investigations that might help distinguish them from microbleeds.

Microbleed mimics either contain blood products, or they do not (instead resembling microbleeds because of shared signal intensity and morphology on GRE MRI). In this chapter, we describe both types of microbleed mimic, outline how these can be differentiated from true brain microbleeds, and suggest a topographical approach to the recognition of microbleed mimics on brain imaging.

Search strategy

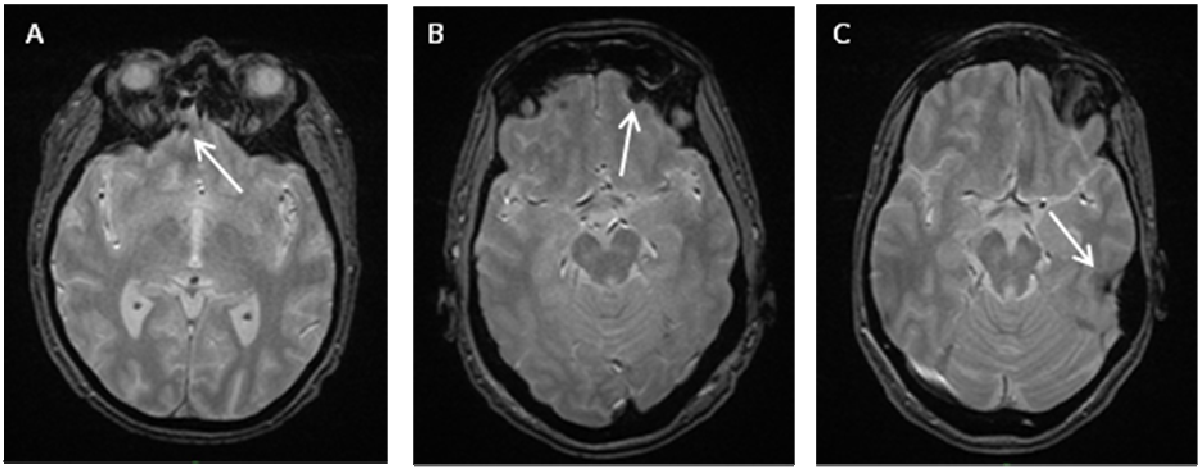
In February 2010, we searched Ovid Medline with an electronic strategy used in a prior systematic review,(2) combined it with the textword 'mimic', and selected pertinent articles for this chapter. We also used our personal bibliographies and experience of identifying microbleed mimics during the development of the Brain Observer Microbleed Scale (BOMBS).(3)

A. Microbleed mimics that do not contain blood products, but with MRI signal properties similar to microbleeds

1. Partial volume artefact

MR images consist of a matrix of picture elements, or pixels, reflecting the content of volume elements, or voxels. Voxel and pixel size influence spatial resolution and thus contrast. All anatomical structures within one voxel add to its averaged signal intensity in the final image. The smaller the voxel size, the better the spatial resolution of the MR image; however, the bigger the voxel size, the better the signal (and signal-to-noise ratio). In general, the signal-to-noise ratio is the determining factor for the final voxel/pixel size. Averaging of signal intensities of different structures within voxels – with loss of contrast between different tissues – is known as partial volume effect. In the brain, partial volume artefact occurring adjacent to the petrous temporal bones, paranasal sinuses, frontal bones, orbit,(3) and occipital bones (4) can lead to small hypointense areas on GRE and T2-weighted imaging (T2WI) which mimic microbleeds (Figure 1). Awareness of the anatomical sites predisposed to partial volume artefacts, and review of adjacent slices in these areas, will reduce misinterpretation of partial volume artefacts as microbleeds.

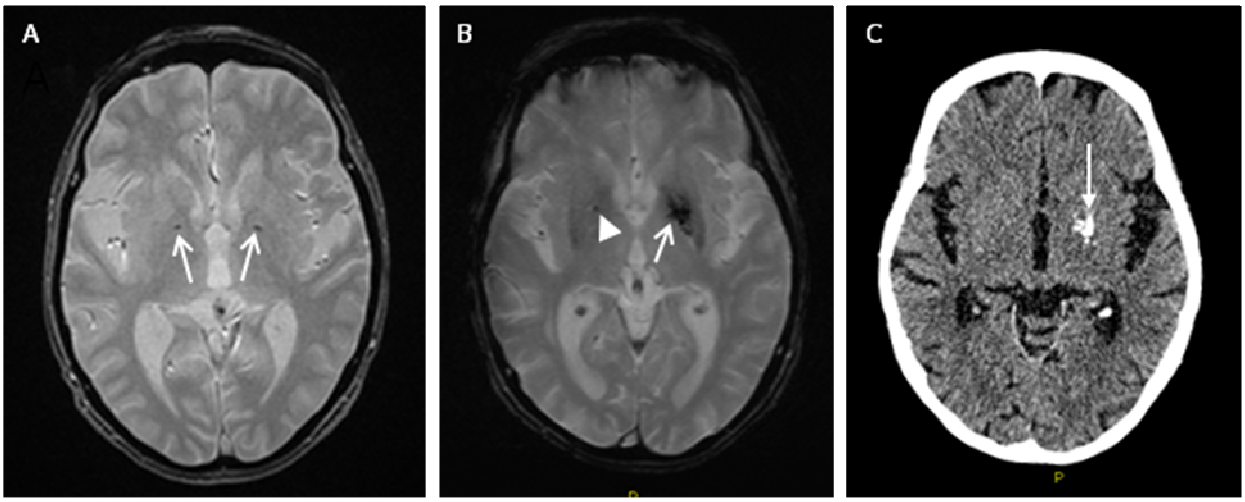
Figure 1. Microbleed mimics due to partial volume artefact on axial GRE MRI, occurring adjacent to the paranasal sinuses (A, arrow), orbit (B, arrow) and petrous temporal bone (C, arrow).



2. Paramagnetic substances

GRE sequences used in the detection of microbleeds are sensitive not only to blood breakdown products (deoxyhaemoglobin, methaemoglobin, haemosiderin and ferritin), but also to other paramagnetic substances such as calcium, manganese and iron, all of which may appear as foci of low signal. Basal ganglia mineralisation is a frequent finding on brain imaging in older adults, and in some cases it is associated with disordered calcium metabolism, extrapyramidal syndromes, or neuropsychiatric disorders.(5) Where basal ganglia mineralisation is suspected, computerised tomography (CT) imaging of the brain may be helpful in identifying calcification (Figure 2), although correlation of suspected basal ganglia calcification on MRI with CT was mentioned in only 14 of 53 studies identified by a systematic review.(2)

Figure 2. Basal ganglia mineralisation mimicking microbleeds. Minor, symmetric basal ganglia mineralisation, with small, solitary foci of low signal on axial GRE magnetic resonance imaging (A, arrows). Asymmetric basal ganglia mineralisation on axial GRE MRI (B), demonstrating multiple hypointense foci on the left (arrow) and a solitary hypointense focus on the right (arrowhead). Axial CT brain in the same patient (C) confirms the presence of calcification in the left basal ganglia (arrow).



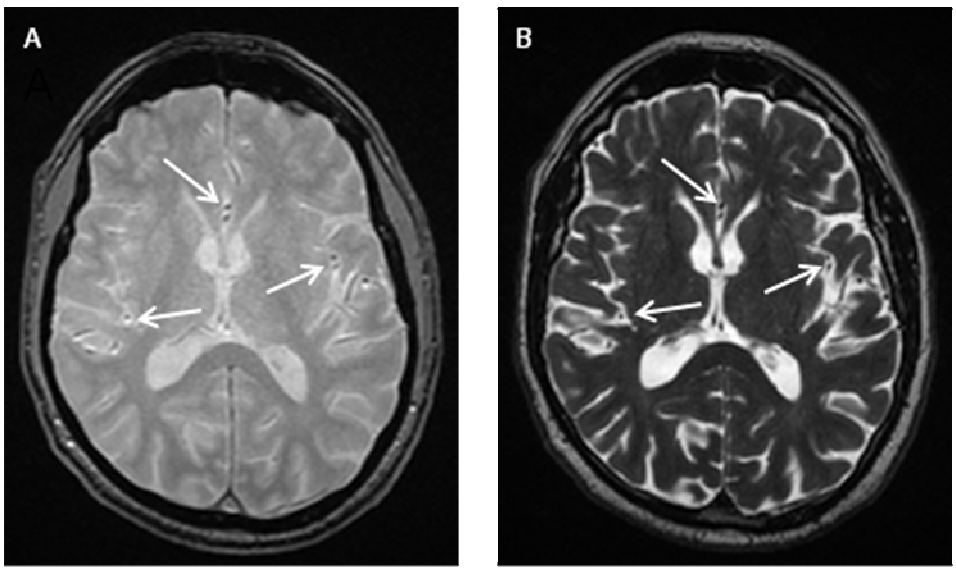
3. Air embolism, iatrogenic devices, and metallic embolism

There has been a single case report of cerebral air emboli causing multiple, bilateral, small round foci of hypointensity on GRE imaging,(6) and there are several descriptions of multifocal GRE hypointensities due to embolisation of metallic fragments from prosthetic heart valves.(7) Non-metallic ventricular shunt tubes in cross-section have been also been reported as potential mimics of microbleeds.(8) In such cases, correlation with the clinical history and review of all MRI sequences, as well as use of other types of imaging (such as plain radiography and CT), should enable these microbleed mimics to be correctly identified.

4. Blood vessels

On GRE imaging, foci of low signal representing vascular flow voids may be mistaken for microbleeds (especially when seen in cross section). Most often, these are flow voids in pial and leptomeningeal vessels in the cerebral sulci, but flow voids in small, deep perforator (lenticulostriate) vessels supplying the deeper structures of the brain may also be mistaken for microbleeds (Figure 3).(3;9) However, in contrast to true microbleeds, flow voids do not demonstrate susceptibility ('blooming') artefact on GRE sequences. Furthermore, flow voids, but not microbleeds, may be seen as linear structures on consecutive axial slices. Careful examination of lesion morphology on consecutive axial slices, and review of T2-weighted imaging (on which vascular flow voids are more easily seen compared to GRE), should help to correctly distinguish small vessel branches from microbleeds situated close to blood vessels.

Figure 3. Flow voids of leptomeningeal vessels imaged in cross section, appearing as punctate foci of hypointensity in the cortical sulci on axial GRE (A) and T2 (B) brain MRI.



B. Microbleed mimics containing blood products

5. Diffuse axonal injury

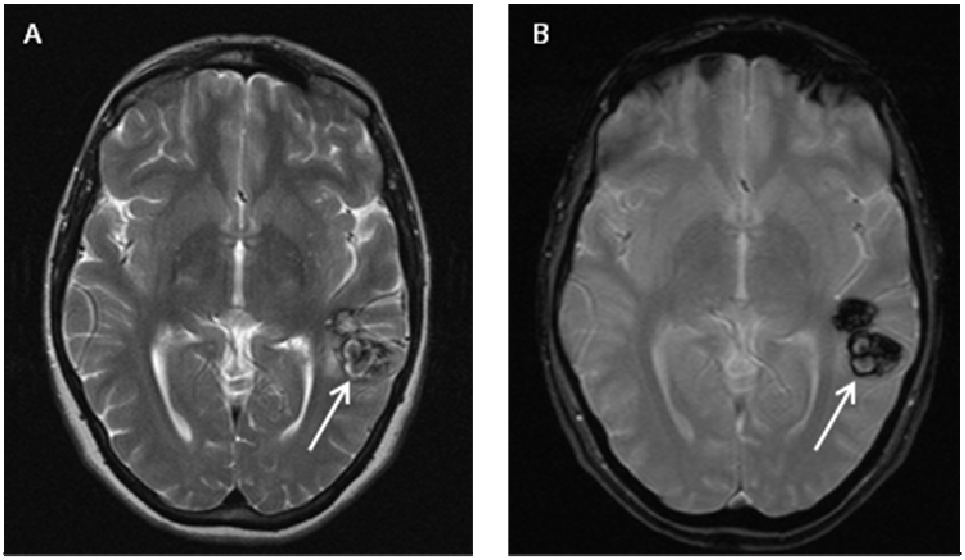
Diffuse axonal injury, a type of traumatic brain injury usually caused by rapid rotational acceleration and deceleration of the brain, leads to shearing of axons in susceptible areas such as the grey-white matter junction, splenium of the corpus callosum, internal capsule and dorsolateral brainstem.(10) Multiple, small hypointensities on T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR) and GRE MRI sequences may appear following diffuse axonal injury.(11) These lesions may be differentiated from microbleeds on the basis of the clinical history as well as other associated imaging abnormalities (such as parenchymal contusions and skull fractures).

6. Cavernous malformations

Cavernous malformations are composed of clusters of thin-walled endothelial vessels, missing components of the blood-brain barrier, without intervening neural tissue.(12) On MRI, their hallmark is a hypointense rim of haemosiderin, within which there is a core of variable signal intensity.(13) On MRI, a mixed signal intensity core (representing haemorrhage in different stages of evolution) gives many cavernous malformations a distinctive 'mulberry' or 'popcorn-like' appearance (Figure 4), but this appearance is type II of four proposed sub-types of *familial* cavernous malformation: type I – subacute haemorrhage; type II – mixed subacute and chronic haemorrhage; type III – chronic haemorrhage; and type IV – punctuate hypointensity.(14) In general, types I–III can usually be distinguished from microbleeds by the presence of blood in various stages of evolution

and a haemosiderin rim on T1- and T2-weighted imaging, but type IV cavernous malformations, appaearing as punctuate hypointensities, exhibit similar signal characteristics to microbleeds on MRI. Some type IV lesions evolve into type I-III lesions over time.(15) However, to what extent type IV lesions are distinct from microbleeds is less clear, especially when they are solitary, or they are unaccompanied by type I-III cavernous malformations, a family history, or a relevant genetic mutation.

Figure 4. Typical 'popcorn-like' appearance of a cavernous malformation on axial T2 (A) and axial GRE (B) brain MRI (arrows).



7. Haemorrhagic metastases

Diffuse haemorrhagic micrometastases, e.g. from renal cell carcinoma or melanoma, may lead to the appearance of multifocal microbleeds.(16) Differentiation of these metastases from microbleeds may be aided by clinical history and careful examination, as well as associated imaging findings such as perilesional oedema (particularly after recent

haemorrhage) and typical signal characteristics of the lesions on other MRI sequences (e.g. T1 hyperintensity in melanomatous deposits (16)).

8. Haemorrhagic transformation of a cerebral infarction

In haemorrhagic transformation of recent infarcts, small (petechial) areas of haemorrhage may be seen within, or along the margin of, the infarct. In most cases, identification of this particular microbleed mimic should be possible from the clinical history and examination, and from associated imaging findings, particularly on diffusion-weighted imaging.(4)

Suggested topographical approach to the interpretation of microbleed mimics

The approach we have outlined to distinguishing microbleeds from mimics on the basis of the presence blood products may be further refined by considering the anatomical location of the abnormalities identified. In lobar regions of the brain (cortical grey matter, subcortical white matter, and grey-white matter junction), common microbleed mimics include vascular flow voids and hypointensities due to partial volume artefact. In deep regions of the brain (basal ganglia, thalamus, and internal and external capsule) mineralisation of the basal ganglia and flow voids from perforating vessels should be considered. Other mimics tend not to be so easily distinguished on anatomical grounds. We have recently devised an online guide to aid the rating and interpretation of microbleeds, which describes our approach to microbleed mimic interpretation, and also highlights difficulties which may be encountered in identifying potentially solitary microbleeds. This is available at http://www.sbirc.ed.ac.uk/imageanalysis.html#bombs.

Future influences on microbleed mimics

The development of susceptibility-weighted imaging (SWI, Chapter 4) has increased the detection of structures containing extravascular blood products, as well as those containing venous deoxygenated blood.(17) SWI may improve the detection of small vascular malformations such as telangiectasia, developmental venous anomalies and dural arteriovenous fistulae when compared to standard MRI sequences. SWI may also help distinguish the diamagnetic and paramagnetic effects of calcium and blood respectively,(18) but whether the greater sensitivity of SWI diminishes or compounds the problem of microbleed mimics in comparison to GRE MRI remains to be determined.

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